ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Round, biconvex, white film-coated tablet debossed with 'GS NX3' and '25' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Revolade is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Revolade may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated.

Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy (see sections 4.4 and 5.1).

Revolade is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation (see section 5.1).

4.2 Posology and method of administration

Eltrombopag treatment should be initiated and remain under the supervision of a physician who is experienced in the treatment of haematological diseases or the management of chronic hepatitis C and its complications.

Posology

Eltrombopag dosing requirements must be individualised based on the patient's platelet counts. The objective of treatment with eltrombopag should not be to normalise platelet counts.

In most patients, measurable elevations in platelet counts take 1-2 weeks (see section 5.1).

Chronic immune (idiopathic) thrombocytopenia

The lowest dose of eltrombopag to achieve and maintain a platelet count ≥ 50,000/µl should be used. Dose adjustments are based upon the platelet count response. Do not use eltrombopag to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting eltrombopag and decreased within 1 to 2 weeks after discontinuation.

The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2).

Monitoring and dose adjustment

After initiating eltrombopag, adjust the dose to achieve and maintain a platelet count ≥ 50,000/µl as necessary to reduce the risk for bleeding. Do not exceed a dose of 75 mg daily.

Clinical haematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dose regimen of eltrombopag modified based on platelet counts as outlined in Table 1. During therapy with eltrombopag full blood counts (FBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count (≥ 50,000/µl for at least 4 weeks) has been achieved. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter.

The lowest effective dosing regimen to maintain platelet counts should be used as clinically indicated.

Table 1 Dose adjustments of eltrombopag in ITP patients

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day.
≥ 50,000/µl to ≤ 150,000/µl	Use lowest dose of eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
> 150,000/µl to ≤ 250,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 250,000/µl	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 25 mg.

Eltrombopag can be administered in addition to other ITP medicinal products. The dose regimen of concomitant ITP medicinal products should be modified, as medically appropriate, to avoid excessive increases in platelet counts during therapy with eltrombopag.

Wait for at least 2 weeks to see the effect of any dose adjustment on the patient's platelet response prior to considering another dose adjustment.

The standard eltrombopag dose adjustment, either decrease or increase, would be 25 mg once daily. However, in a few patients a combination of different film-coated tablet strengths on different days may be required.

Discontinuation

Treatment with eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of eltrombopag therapy at 75 mg once daily.

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician. The reoccurrence of thrombocytopenia is possible upon discontinuation of treatment (see section 4.4).

Chronic hepatitis C (HCV) associated thrombocytopenia

When eltrombopag is given in combination with antivirals reference should be made to the full summary of product characteristics of the respective coadministered medicinal products for comprehensive details of relevant safety information or contraindications.

In clinical studies, platelet counts generally began to increase within 1 week of starting eltrombopag. The aim of treatment with eltrombopag should be to achieve the minimum level of platelet counts needed to initiate antiviral therapy, in adherence to clinical practice recommendations. During antiviral therapy, the aim of treatment should be to keep platelet counts at a level that prevents the risk of bleeding complications, normally around 50,000-75,000/µl. Platelet counts > 75,000/µl should be avoided. The lowest dose of eltrombopag needed to achieve the targets should be used. Dose adjustments are based upon the platelet count response.

Initial dose regimen

Eltrombopag should be initiated at a dose of 25 mg once daily. No dosage adjustment is necessary for HCV patients of East Asian ancestry or patients with mild hepatic impairment (see section 5.2).

Monitoring and dose adjustment

The dose of eltrombopag should be adjusted in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate anti-viral therapy. Platelet counts should be monitored every week prior to starting antiviral therapy. On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose adjustments should be avoided (see Table 2).

During antiviral therapy, the dose of eltrombopag should be adjusted as necessary to avoid dose reductions of peginterferon due to decreasing platelet counts that may put patients at risk of bleeding (see Table 2). Platelet counts should be monitored weekly during antiviral therapy until a stable platelet count is achieved, normally around 50,000-75,000/µl. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter. Dose reductions on the daily dose by 25 mg should be considered if platelet counts exceed the required target. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.

Do not exceed a dose of 100 mg eltrombopag once daily.

Table 2 Dose adjustments of eltrombopag in HCV patients during antiviral therapy

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 100 mg/day.
≥ 50,000/µl to ≤ 100,000/µl	Use lowest dose of eltrombopag as necessary to avoid dose reductions of peginterferon
> 100,000/µl to ≤ 150,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments♦.
> 150,000/µl	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 25 mg*.

* - For patients taking 25 mg eltrombopag once daily, consideration should be given to reinitiating dosing at 25 mg every other day.

♦ - On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose reductions should be avoided.

Discontinuation

If after 2 weeks of eltrombopag therapy at 100 mg the required platelet level to initiate antiviral therapy is not achieved, eltrombopag should be discontinued.

Eltrombopag treatment should be terminated when antiviral therapy is discontinued unless otherwise justified. Excessive platelet count responses or important liver test abnormalities also necessitate discontinuation.

Severe Aplastic Anaemia

Initial Dose Regimen

Initiate eltrombopag at a dose of 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2). The treatment should not be initiated when the patients have existing cytogenetic abnormalities of chromosome 7.

Monitoring and dose adjustment

Haematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting eltrombopag (see section 5.1). Adjust the dose of eltrombopag in 50 mg increments every 2 weeks as necessary to achieve the target platelet count ≥ 50,000/µl. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg. Do not exceed a dose of 150 mg daily. Monitor clinical haematology and liver tests regularly throughout therapy with eltrombopag and modify the dosage regimen of eltrombopag based on platelet counts as outlined in Table 3.

Table 3 Dose adjustments of eltrombopag in patients with severe aplastic anaemia

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg.
≥ 50,000/µl to ≤ 150,000/µl	Use lowest dose of eltrombopag to maintain platelet counts.
> 150,000/µl to ≤ 250,000/µl	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 250,000/µl	Stop eltrombopag; for at least one week. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 50 mg.

Tapering for tri-lineage (white blood cells, red blood cells, and platelets) responders

For patients who achieve tri-lineage response, including transfusion independence, lasting at least 8 weeks: the dose of eltrombopag may be reduced by 50 %.

If counts remain stable after 8 weeks at the reduced dose, then discontinue eltrombopag and monitor blood counts. If platelet counts drop to < 30,000/µl, haemoglobin to < 9 g/dL or ANC < 0.5 x 10^9/L, eltrombopag may be reinitiated at the previous effective dose.

Discontinuation

If no haematological response has occurred after 16 weeks of therapy with eltrombopag, discontinue therapy. If new cytogenetic abnormalities are detected, evaluate whether continuation of eltrombopag is appropriate *(*see sections 4.4 and 4.8). Excessive platelet count responses (as outlined in Table 3) or important liver test abnormalities also necessitate discontinuation of eltrombopag (see section 4.8).

Special populations

Renal impairment

No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis (see section 5.2).

Hepatic impairment

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see section 4.4).

If the use of eltrombopag is deemed necessary for ITP patients with hepatic impairment the starting dose must be 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment wait 3 weeks before increasing the dose.

No dose adjustment is required for thrombocytopenic patients with chronic HCV and mild hepatic impairment (Child-Pugh score ≤ 6). Chronic HCV patients and severe aplastic anaemia patients with hepatic impairment should initiate eltrombopag at a dose of 25 mg once daily (see section 5.2). After initiating the dose of eltrombopag in patients with hepatic impairment wait 2 weeks before increasing the dose.

There is an increased risk for adverse events, including hepatic decompensation and thromboembolic events, in thrombocytopenic patients with advanced chronic liver disease treated with eltrombopag, either in preparation for invasive procedure or in HCV patients undergoing antiviral therapy (see sections 4.4 and 4.8).

Elderly

There are limited data on the use of eltrombopag in ITP patients aged 65 years and older and no clinical experience in ITP patients aged over 85 years. In the clinical studies of eltrombopag, overall no clinically significant differences in safety of eltrombopag were observed between subjects aged at least 65 years and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see section 5.2).

There are limited data on the use of eltrombopag in HCV and SAA patients aged over 75 years. Caution should be exercised in these patients (see section 4.4).

East Asian patients

For patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), including those with hepatic impairment, eltrombopag should be initiated at a dose of 25 mg once daily (see section 5.2).

Patient platelet count should continue to be monitored and the standard criteria for further dose modification followed.

Paediatric population

The safety and efficacy of eltrombopag has not been established in children and adolescents (< 18 years). No data are available.

Method of administration

Oral use. Eltrombopag should be taken at least four hours before or after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminium, selenium and zinc) (see sections 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to eltrombopag or to any of the excipients, listed in section 6.1.

4.4 Special warnings and precautions for use

There is an increased risk for adverse reactions, including potentially fatal hepatic decompensation and thromboembolic events, in thrombocytopenic HCV patients with advanced chronic liver disease, as defined by low albumin levels ≤ 35 g/L or MELD score ≥ 10, when treated with eltrombopag in combination with interferon-based therapy. In addition, the benefits of treatment in terms of the proportion achieving sustained virological response (SVR) compared with placebo were modest in these patients (especially for those with baseline albumin ≤ 35g/L) compared with the group overall. Treatment with eltrombopag in these patients should be initiated only by physicians experienced in the management of advanced HCV, and only when the risks of thrombocytopenia or withholding antiviral therapy necessitate intervention. If treatment is considered clinically indicated, close monitoring of these patients is required.

Combination with direct acting antiviral agents

Safety and efficacy have not been established in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C infection.

Risk of hepatotoxicity

Eltrombopag administration can cause abnormal liver function. In the controlled clinical studies in chronic ITP with eltrombopag, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin were observed (see section 4.8).

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function. Across the 3 placebo-controlled studies in chronic ITP, 1 patient in the placebo group and 1 patient in the eltrombopag group experienced a Grade 4 liver test abnormality.

In 2 controlled clinical studies in patients with HCV, ALT or AST ≥ 3 x ULN was reported in 34 % and 38 % of the eltrombopag and placebo groups, respectively. Most patients receiving eltrombopag in combination with peginterferon / ribavirin therapy will experience indirect hyperbilirubinaemia. Overall, total bilirubin ≥ 1.5 x ULN was reported in 76 % and 50 % of the eltrombopag and placebo groups, respectively.

Serum ALT, AST and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinaemia. If bilirubin is elevated perform fractionation. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilise, or return to baseline levels. Eltrombopag should be discontinued if ALT levels increase (≥ 3X ULN in patients with normal liver function or ≥ 3X baseline in patients with pre-treatment elevations in transaminases) and are:

- progressive, or
- persistent for ≥ 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

Exercise caution when administering eltrombopag to patients with hepatic disease. In ITP and SAA patients use a lower starting dose of eltrombopag and monitor closely when administering to patients with hepatic impairment (see section 4.2).

Hepatic decompensation (use with interferon)

Hepatic decompensation in patients with chronic hepatitis C: Monitor patients with low albumin levels (≤ 35 g/L) or with Model for End Stage Liver Disease (MELD) score ≥ 10 at baseline.

Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently in the eltrombopag arm (11 %) than in the placebo arm (6 %). In patients with low albumin levels (≤ 35 g/L) or MELD score ≥ 10 at baseline, there was a three-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. In addition, the benefits of treatment in terms of the proportion achieving SVR compared with placebo were modest in these patients (especially for those with baseline albumin ≤ 35g/L) compared with the group overall. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. The respective interferon summary of product characteristics should be referenced for discontinuation criteria. Eltrombopag should be terminated if antiviral therapy is discontinued for hepatic decompensation.

Thrombotic/Thromboembolic complications

In controlled studies in thrombocytopenic patients with HCV receiving interferon-based therapy (n = 1439), 38 out of 955 subjects (4 %) treated with eltrombopag and 6 out of 484 subjects (1 %) in the placebo group experienced thromboembolic events (TEEs). Reported thrombotic/thromboembolic complications included both venous and arterial events. The majority of TEEs were non-serious and resolved by the end of the study. Portal vein thrombosis was the most common TEE in both treatment groups (2 % in patients treated with eltrombopag versus < 1 % for placebo). No specific temporal relationship between start of treatment and event of TEE were observed. Patients with low albumin levels (≤ 35 g/L) or MELD ≥ 10 had a twofold greater risk of TEEs than those with higher albumin levels; those aged ≥ 60 years had a 2-fold greater risk of TEEs compared to younger patients. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients should be closely monitored for signs and symptoms of TEE.

The risk of TEEs has been found to be increased in patients with chronic liver disease (CLD) treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures. Six of 143 (4 %) adult patients with CLD receiving eltrombopag experienced TEEs (all of the portal venous system) and two of 145 (1 %) subjects in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five of the 6 patients treated with eltrombopag experienced the thrombotic complication at a platelet count > 200,000/µl and within 30 days of the last dose of eltrombopag. Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures.

In eltrombopag clinical trials in ITP thromboembolic events were observed at low and normal platelet counts. Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism including but not limited to inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing eltrombopag treatment if the platelet count exceeds the target levels (see section 4.2). The risk-benefit balance should be considered in patients at risk of thromboembolic events (TEEs) of any aetiology.

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate, exercise caution when administering eltrombopag to patients with hepatic impairment (see sections 4.2 and 4.8).

Bleeding following discontinuation of eltrombopag

Thrombocytopenia is likely to reoccur in ITP patients upon discontinuation of treatment with eltrombopag. Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increase the bleeding risk and in some cases may lead to bleeding. This risk is increased if eltrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with eltrombopag is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support. Platelet counts must be monitored weekly for 4 weeks following discontinuation of eltrombopag.

In HCV clinical trials, a higher incidence of gastrointestinal bleeding, including serious and fatal cases, was reported following discontinuation of peginterferon, ribavirin, and eltrombopag. Following discontinuation of therapy, patients should be monitored for any signs or symptoms of gastrointestinal bleeding.

Bone marrow reticulin formation and risk of bone marrow fibrosis

Eltrombopag may increase the risk for development or progression of reticulin fibres within the bone marrow. The relevance of this finding, as with other thrombopoietin receptor (TPO-R) agonists, has not been established yet.

Prior to initiation of eltrombopag, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, full blood count (FBC) with white blood cell count (WBC) differential should be performed monthly. If immature or dysplastic cells are observed, peripheral blood smears should be examined for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), treatment with eltrombopag should be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

Progression of existing Myelodysplastic Syndrome (MDS)

TPO-R agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO-R is predominantly expressed on the surface of cells of the myeloid lineage. For TPO-R agonists there is a concern that they may stimulate the progression of existing haematopoietic malignancies such as MDS.

In clinical studies with a TPO-R agonist in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to acute myeloid leukaemia (AML) were reported.

The diagnosis of ITP or SAA in adults and elderly patients should be confirmed by the exclusion of other clinical entities presenting with thrombocytopenia, in particular the diagnosis of MDS must be excluded. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms, or abnormal signs such as increased peripheral blast cells.

The effectiveness and safety of eltrombopag have not been established for use in other thrombocytopenic conditions including chemotherapy-induced thrombocytopenia or MDS. Eltrombopag should not be used outside of clinical trials for the treatment of thrombocytopenia due to MDS or any other cause of thrombocytopenia other than the approved indications.

Cytogenetic abnormalities and progression to MDS/AML in patients with SAA:

Cytogenetic abnormalities are known to occur in SAA patients. It is not known whether eltrombopag increases the risk of cytogenetic abnormalities in patients with SAA. In the phase II SAA clinical study with eltrombopag, the incidence of new cytogenetic abnormalities was observed in 19% of patients [8/43 (where 5 of them had changes in chromosome 7)]. The median time on study to a cytogenetic abnormality was 2.9 months.

In clinical trials with eltrombopag in SAA, 4% of patients (5/133) were diagnosed with MDS. The median time to diagnosis was 3 months from the start of eltrombopag treatment.

For SAA patients refractory to or heavily pretreated with prior immunosuppressive therapy, bone marrow examination with aspirations for cytogenetics is recommended prior to initiation of eltrombopag, at 3 months of treatment and 6 months thereafter. If new cytogenetic abnormalities are detected, evaluate whether continuation of eltrombopag is appropriate.

Ocular changes

Cataracts were observed in toxicology studies of eltrombopag in rodents (see section 5.3). In controlled studies in thrombocytopenic patients with HCV receiving interferon therapy (n = 1439), progression of pre-existing baseline cataract(s) or incident cataracts was reported in 8 % of the eltrombopag group and 5 % of the placebo group. Retinal haemorrhages, mostly Grade 1 or 2, have been reported in HCV patients receiving interferon, ribavirin and eltrombopag (2 % of the eltrombopag group and 2 % of the placebo group. Haemorrhages occurred on the surface of the retina (preretinal), under the retina (subretinal), or within the retinal tissue. Routine ophthalmologic monitoring of patients is recommended.

QT/QTc prolongation

A QTc study in healthy volunteers dosed 150 mg eltrombopag per day did not show a clinically significant effect on cardiac repolarisation. QTc interval prolongation has been reported in clinical trials of patients with ITP and thrombocytopenic patients with HCV. The clinical significance of these QTc prolongation events is unknown.

Loss of response to eltrombopag

A loss of response or failure to maintain a platelet response with eltrombopag treatment within the recommended dosing range should prompt a search for causative factors, including an increased bone marrow reticulin.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of eltrombopag on other medicinal products

HMG CoA reductase inhibitors

In vitro studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter. *In vitro* studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor. Administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin C_{max} 103 % (90 % confidence interval [CI]: 82 %, 126 %) and $AUC_{0-\infty}$ 55 % (90 % CI: 42 %, 69 %). Interactions are also expected with other HMG-CoA reductase inhibitors, including atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin. When co-administered with eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken (see section 5.2).

OATP1B1 and BCRP substrates

Concomitant administration of eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should be undertaken with caution (see section 5.2).

Cytochrome P450 substrates

In studies utilizing human liver microsomes, eltrombopag (up to 100 μM) showed no *in vitro* inhibition of the CYP450 enzymes 1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11 and was an inhibitor of CYP2C8 and CYP2C9 as measured using paclitaxel and diclofenac as the probe substrates. Administration of eltrombopag 75 mg once daily for 7 days to 24 healthy male subjects did not inhibit or induce the metabolism of probe substrates for 1A2 (caffeine), 2C19 (omeprazole), 2C9 (flurbiprofen), or 3A4 (midazolam) in humans. No clinically significant interactions are expected when eltrombopag and CYP450 substrates are co-administered (see section 5.2).

HCV Protease Inhibitors

Dose adjustment is not required when eltrombopag is co-administered with either telaprevir or boceprevir. Co-administration of a single dose of eltrombopag 200 mg with telaprevir 750 mg Q8h did not alter plasma telaprevir exposure.

Co-administration of a single dose of eltrombopag 200 mg with boceprevir 800 mg Q8h did not alter plasma boceprevir $AUC_{(0-\tau)}$, but increased C_{max} by 20 %, and decreased C_{min} by 32 %. The clinical relevance of the decrease in C_{min} has not been established, increased clinical and laboratory monitoring for HCV suppression is recommended.

Effects of other medicinal products on eltrombopag

Polyvalent cations (chelation)

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc. Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-\infty}$ by 70 % (90 % CI: 64 %, 76 %) and C_{max} by 70 % (90 % CI: 62 %, 76 %). Antacids, dairy products and other products containing polyvalent cations, such as mineral supplements, must be administered at least four hours apart from eltrombopag dosing to avoid significant reduction in eltrombopag absorption due to chelation (see sections 4.2 and 5.2).

Food interaction

Administration of a single 50 mg-dose of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag $AUC_{0-\infty}$ by 59 % (90 % CI: 54 %, 64 %) and C_{max} by 65 % (90 % CI: 59 %, 70 %). Food low in calcium [< 50 mg calcium] including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see sections 4.2 and 5.2).

Lopinavir/ritonavir

Co-administration of eltrombopag with lopinavir/ritonavir (LPV/RTV) may cause a decrease in the concentration of eltrombopag. A study in 40 healthy volunteers showed that the co-administration of single dose eltrombopag 100 mg with repeat dose LPV/RTV 400 /100 mg twice daily resulted in a reduction in eltrombopag plasma $AUC_{(0-\infty)}$ by 17 % (90 % CI: 6.6 %, 26.6 %). Therefore, caution should be used when co-administration of eltrombopag with LPV/RTV takes place. Platelet count should be closely monitored in order to ensure appropriate medical management of the dose of eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued.

CYP1A2 and CYP2C8 inhibitors and inducers

Eltrombopag is metabolized through multiple pathways including CYP1A2, CYP2C8, UGT1A1, and UGT1A3 (see section 5.2). Medicinal products that inhibit or induce a single enzyme are unlikely to significantly affect plasma eltrombopag concentrations; whereas medicinal products that inhibit or induce multiple enzymes have the potential to increase (e.g. fluvoxamine) or decrease (e.g. rifampicin) eltrombopag concentrations.

HCV Protease Inhibitors

Results of a drug-drug pharmacokinetic (PK) interaction study show that co-administration of repeat doses of boceprevir 800 mg Q8h or telaprevir 750 mg Q8h with a single dose of eltrombopag 200 mg did not alter plasma eltrombopag exposure to a clinically significant extent.

Medicinal products for treatment of ITP

Medicinal products used in the treatment of ITP in combination with eltrombopag in clinical studies included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Platelet counts should be monitored when combining eltrombopag with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of eltrombopag in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Revolade is not recommended during pregnancy.

Women of childbearing potential / Contraception in males and females

Revolade is not recommended in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether eltrombopag/metabolites are excreted in human milk. Studies in animals have shown that eltrombopag is likely secreted into milk (see section 5.3); therefore a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to continue/abstain from Revolade therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Fertility was not affected in male or female rats at exposures that were comparable to those in humans. However a risk for humans cannot be ruled out (see section 5.3).

4.7 Effects on ability to drive and use machines

Eltrombopag has negligible influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of eltrombopag, including dizziness and lack of alertness, should be borne in mind when considering the patient's ability to perform tasks that require judgment, motor and cognitive skills.

4.8 Undesirable effects

Summary of safety profile

Based on an analysis of all chronic ITP patients receiving eltrombopag in 4 controlled and 2 uncontrolled clinical studies, the overall incidence of adverse reactions in subjects treated with eltrombopag was 79 % (433/530). The mean duration of exposure to eltrombopag was 260 days and patient year's exposure was 390 in this study population.

ENABLE 1 (TPL103922 N=716) and ENABLE 2 (TPL108390 N=805) were randomized, double-blind, placebo-controlled, multicentre studies to assess the efficacy and safety of eltrombopag in thrombocytopenic subjects with HCV infection who were otherwise eligible to initiate antiviral therapy with interferon and ribavirin therapy.

In the HCV studies the safety population consisted of all randomized subjects who received double-blind study drug during Part 2 of ENABLE 1 (eltrombopag treatment N=449, placebo N=232) and ENABLE 2 (eltrombopag treatment N=506, placebo N=252). Subjects are analysed according to the treatment received (total safety double blind population, eltrombopag N=955 and placebo N=484).

The safety of eltrombopag in severe aplastic anaemia was assessed in a single-arm, open-label trial (N=43) in which 12 patients (28 %) were treated for > 6 months and 9 patients (21 %) were treated for > 1 year.

The most important serious adverse reactions identified in the ITP or HCV trials were hepatotoxicity and thrombotic/thromboembolic events.

The most common adverse reactions (experienced by at least 10 % of patients) of any grade in the ITP or HCV trials included; headache, anaemia, decreased appetite, insomnia, cough, nausea, diarrhoea, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza like illness, asthenia, chills and peripheral oedema.

List of adverse reactions

The adverse reactions in the ITP studies (N = 550), the HCV studies (N = 955), the SAA studies (N = 43) and post-marketing reports are listed below by MedDRA system organ class and by frequency.

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1,000 to < 1/100)
Rare	(≥ 1/10,000 to < 1/1,000)
Very rare	(< 1/10,000)
Not known	(cannot be estimated from the available data)

ITP study population

Infections and infestations

Uncommon Pharyngitis, Urinary tract infection, Influenza, Oral herpes, Pneumonia, Sinusitis, Tonsillitis, Respiratory tract infection, Gingivitis, Skin infection

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Uncommon Rectosigmoid cancer

Blood and lymphatic system disorders

Uncommon Anaemia, Anisocytosis, Eosinophilia, Haemolytic anaemia, Leukocytosis, Myelocytosis, Thrombocytopenia, Haemoglobin increased, Band neutrophil count increased, Haemoglobin decreased, Myelocyte present, Platelet count increased, White blood cell count decreased

Immune system disorders

Uncommon Hypersensitivity

Metabolism and nutrition disorders

Uncommon Anorexia, Hypokalaemia, Decreased appetite, Gout, Hypocalcaemia, Blood uric acid increased

Psychiatric disorders

Uncommon Sleep disorder, Depression, Apathy, Mood altered, Tearfulness

Nervous systems disorders

Common Paraesthesia

Uncommon Hypoaesthesia, Somnolence, Migraine, Tremor, Balance disorder, Dysaesthesia, Hemiparesis, Migraine with aura, Neuropathy peripheral, Peripheral sensory neuropathy, Speech disorder, Toxic neuropathy, Vascular headache

Eye disorders

Common Dry eye

Uncommon Vision blurred, Lenticular opacities, Astigmatism, Cataract cortical, Eye pain, Lacrimation increased, Retinal haemorrhage, Retinal pigment epitheliopathy, Visual acuity reduced, Visual impairment, Visual acuity tests abnormal, Blepharitis and Keratoconjunctivitis sicca

Ear and labyrinth disorders

Uncommon Ear pain, Vertigo

Cardiac disorders

Uncommon Tachycardia, Acute myocardial infarction, Cardiovascular disorder, Cyanosis, Sinus tachycardia, Electrocardiogram QT prolonged

Vascular disorders

Uncommon Deep vein thrombosis, Embolism, Hot flush, Thrombophlebitis superficial, Flushing, Haematoma

Respiratory, thoracic and mediastinal disorders

Uncommon Pulmonary embolism, Pulmonary infarction, Nasal discomfort, Oropharyngeal blistering, Oropharyngeal pain, Sinus disorder, Sleep apnoea syndrome

Gastrointestinal disorders

Common Nausea, Diarrhoea, Mouth ulceration

Uncommon Dry mouth, Vomiting, Abdominal pain, Glossodynia, Mouth haemorrhage, Abdominal tenderness, Faeces discoloured, Flatulence, Food poisoning, Frequent bowel movements, Haematemesis, Oral discomfort

Hepatobiliary disorders

Common Alanine aminotransferase increased*, Aspartate aminotransferase increased*, Hyperbilirubinaemia, Hepatic function abnormal

Uncommon Cholestasis, Hepatic lesion, Hepatitis

*Increase of alanine aminotransferase and aspartate aminotransferase may occur simultaneously, although at a lower frequency.

Skin and subcutaneous tissue disorders

Common Rash, Alopecia

Uncommon Hyperhidrosis, Pruritus generalised, Urticaria, Dermatosis, Petechiae, Cold sweat, Erythema, Melanosis, Pigmentation disorder, Skin discolouration, Skin exfoliation

Musculoskeletal and connective tissue disorders

Common Myalgia, Muscle spasm, Musculoskeletal pain, Bone pain, Back pain

Uncommon Muscular weakness

Renal and urinary disorders

Uncommon Renal failure, Leukocyturia, Lupus nephritis, Nocturia, Proteinuria, Blood urea increased, Blood creatinine increased, Urine protein/creatinine ratio increased

Reproductive system and breast disorders

Common Menorrhagia

General disorders and administration site conditions

Uncommon Chest pain, Feeling hot, Vessel puncture site haemorrhage, Asthenia, Feeling jittery, Inflammation of wound, Malaise, Pyrexia, Sensation of foreign body

Investigations

Uncommon Blood albumin increased, Blood alkaline phosphatase increased, Protein total increased, Blood albumin decreased, pH urine increased

Injury, poisoning and procedural complications

Uncommon Sunburn

HCV study population (in combination with anti-viral interferon and ribavirin therapy)

Infections and infestations

Common Urinary tract infection, Upper respiratory tract infection, Bronchitis, Nasopharyngitis, Influenza, Oral herpes, Gastroenteritis, Pharyngitis

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Common Hepatic neoplasm malignant

Blood and lymphatic system disorders

Very common Anaemia
Common Lymphopenia, Haemolytic anaemia

Metabolism and nutrition disorders

Very common Decreased appetite
Common Hyperglycaemia, Abnormal loss of weight

Psychiatric disorders

Very common Insomnia
Common Depression, Anxiety, Sleep disorder, Confusional state, Agitation

Nervous systems disorders

Very common Headache
Common Dizziness, Disturbance in attention, Dysgeusia, Hepatic encephalopathy, Lethargy, Memory impairment, Paraesthesia

Eye disorders

Common Cataract, Retinal exudates, Dry Eye, Ocular icterus, Retinal haemorrhage

Ear and labyrinth disorders

Common Vertigo

Cardiac disorders

Common Palpitations

Respiratory, thoracic and mediastinal disorders

Very common Cough
Common Dyspnoea, Oropharyngeal pain, Dyspnoea exertional, Productive cough

Gastrointestinal disorders

Very common Nausea, Diarrhoea
Common Vomiting, Ascites, Abdominal pain, Abdominal pain upper, Dyspepsia, Dry mouth, Constipation, Abdominal distension, Toothache, Stomatitis, Gastrooesophagal reflux disease, Haemorrhoids, Abdominal discomfort, Gastritis, Varices oesophageal, Aphthous stomatitis, Oesophageal varices haemorrhage

Hepatobiliary disorders

Common Hyperbilirubinaemia, Jaundice, Portal vein thrombosis, Hepatic failure

Skin and subcutaneous tissue disorders

Very common Pruritus, Alopecia
Common Rash, Dry skin, Eczema, Rash pruritic, Erythema, Hyperhidrosis, Pruritus generalised, Night sweats, Skin lesion

Musculoskeletal and connective tissue disorder

Very common Myalgia
Common Arthralgia, Muscle spasms, Back pain, Pain in extremity, Musculoskeletal pain, Bone pain

Renal and urinary disorders

Uncommon Dysuria

General disorders and administration site conditions

Very common Pyrexia, Fatigue, Influenza like illness, Asthenia, Chills, Oedema peripheral
Common Irritability, Pain, Malaise, Injection site reaction, Non-cardiac chest pain, Oedema, Injection site rash, Chest discomfort, Injection site pruritus

Investigations

Common Blood bilirubin increased, Weight decreased, White blood cell count decreased, Haemoglobin decreased, Neutrophil count decreased, International normalised ratio increased, Activated partial thromboplastin time prolonged, Blood glucose increased, Blood albumin decreased, Electrocardiogram QT prolonged

SAA study population

Blood and lymphatic system disorders

Common Neutropenia, Splenic infarction

Metabolism and nutrition disorders

Common Iron overload, Decreased appetite, Hypoglycaemia, Increased appetite

Psychiatric disorders

Very common Insomnia

Common Anxiety, Depression

Nervous systems disorders

Very common Headache, Dizziness

Common Syncope

Eye disorders

Common Dry eye, Eye pruritus, Cataract, Ocular icterus, Vision blurred, Visual impairment, Vitreous floaters

Respiratory, thoracic and mediastinal disorders

Very common Cough. Dyspnoea, Oropharyngeal Pain, Rhinorrhoea

Common Epistaxis

Gastrointestinal disorders

Very common Abdominal pain, Diarrhoea, Nausea

Common Gingival bleeding, Oral mucosal blistering, Oral pain, Vomiting, Abdominal discomfort, Abdominal pain, Constipation, Abdominal distension, Dysphagia, Faeces discoloured, Swollen tongue, Gastrointestinal motility disorder, Flatulence

Hepatobiliary disorders

Very common Transaminases increased

Common Blood bilirubin increased (hyperbilirubinemia), Jaundice

Skin and subcutaneous tissue disorders

Very common	Ecchymosis
Common	Petechiae, Rash, Pruritus, Urticaria, Skin lesion, Rash Macular

Musculosketal and connective tissue disorders

Very common	Arthralgia, Muscle spasms, Pain in extremity
Common	Back pain, Myalgia, Bone pain

Renal and urinary disorders

Common	Chromaturia

General disorders and administration site conditions

Very common	Fatigue, Febrile neutropenia, Pyrexia
Common	Asthenia, Oedema peripheral, Chills, Malaise

Investigations

Common	Blood creatine phosphokinase increased

Description of selected adverse reactions

Thrombotic/Thromboembolic events (TEEs)

In 3 controlled and 2 uncontrolled clinical studies, among adult chronic ITP patients receiving eltrombopag (n = 446), 17 subjects experienced a total of 19 TEEs, which included (in descending order of occurrence) deep vein thrombosis (n = 6), pulmonary embolism (n = 6), acute myocardial infarction (n = 2), cerebral infarction (n = 2), embolism (n = 1) (see section 4.4).

In a placebo-controlled study (n = 288, Safety population), following 2 weeks treatment in preparation for invasive procedures, 6 of 143 (4 %) adult patients with chronic liver disease receiving eltrombopag experienced 7 TEEs of the portal venous system and 2 of 145 (1 %) subjects in the placebo group experienced 3 TEEs. Five of the 6 patients treated with eltrombopag experienced the TEE at a platelet count > 200,000/µl

No specific risk factors were identified in those subjects who experienced a TEE with the exception of platelet counts ≥ 200,000/µl (see section 4.4).

In controlled studies in thrombocytopenic patients with HCV (n = 1439), 38 out of 955 subjects (4 %) treated with eltrombopag experienced a TEE and 6 out of 484 subjects (1 %) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (2 % in patients treated with eltrombopag versus < 1 % for placebo) (see section 4.4). Patients with low albumin levels (≤ 35 g/L) or MELD ≥ 10 had a twofold greater risk of TEEs than those with higher albumin levels; those aged ≥ 60 years had a 2-fold greater risk of TEEs compared to younger patients.

Hepatic decompensation (use with interferon)

Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently in the eltrombopag arm (11 %) than in the placebo arm (6 %). In patients with low albumin levels (≤ 35 g/L) or Model for End-Stage Liver Disease (MELD) score ≥ 10 at baseline, there was a three-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation (see section 4.4).

Thrombocytopenia following discontinuation of treatment

In the 3 controlled clinical ITP studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8 % and 8 % of the eltrombopag and placebo groups, respectively (see section 4.4).

Increased bone marrow reticulin

Across the programme, no patients had evidence of clinically relevant bone marrow abnormalities or clinical findings that would indicate bone marrow dysfunction. In one ITP patient, eltrombopag treatment was discontinued due to bone marrow reticulin (see section 4.4).

Cytogenetic abnormalities

In the single-arm, open-label trial in SAA, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight (19%) patients had a new cytogenetic abnormality reported, including 5 patients who had changes in chromosome 7. In the two ongoing studies (ELT116826 and ELT116643), cytogenetic abnormalities have been detected in 4/28 (14%) and 4/62 (6%) subjects in each study.

Haematologic malignancies

In the single-arm, open label trial in SAA, three (7%) patients were diagnosed with MDS following treatment with eltrombopag, in the two ongoing studies (ELT116826 and ELT116643), 1/28 (4%) and 1/62 (2%) subject has been diagnosed with MDS or AML in each study.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, consider oral administration of a metal cation-containing preparation, such as calcium, aluminium, or magnesium preparations to chelate eltrombopag and thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with eltrombopag in accordance with dosing and administration recommendations (see section 4.2).

In the clinical studies there was one report of overdose where the subject ingested 5000 mg of eltrombopag. Reported adverse reactions included mild rash, transient bradycardia, ALT and AST elevation, and fatigue. Liver enzymes measured between Days 2 and 18 after ingestion peaked at a 1.6-fold ULN in AST, a 3.9-fold ULN in ALT, and a 2.4-fold ULN in total bilirubin, The platelet counts were 672,000/µl on day 18 after ingestion and the maximum platelet count was 929,000/µl. All events were resolved without sequelae following treatment.

Because eltrombopag is not significantly renally excreted and is highly bound to plasma proteins, haemodialysis would not be expected to be an effective method to enhance the elimination of eltrombopag.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, other systemic hemostatics. ATC code: B02BX 05.

Mechanism of action

TPO is the main cytokine involved in regulation of megakaryopoiesis and platelet production, and is the endogenous ligand for the TPO-R. Eltrombopag interacts with the transmembrane domain of the human TPO-R and initiates signalling cascades similar but not identical to that of endogenous thrombopoietin (TPO), inducing proliferation and differentiation from bone marrow progenitor cells.

Clinical efficacy and safety

Chronic immune (idiopathic) thrombocytopenia (ITP) studies

Two Phase III, randomised, double-blind, placebo-controlled studies RAISE (TRA102537) and TRA100773B and two open-label studies REPEAT (TRA108057) and EXTEND (TRA105325) evaluated the safety and efficacy of eltrombopag in adult patients with previously treated chronic ITP. Overall, eltrombopag was administered to 277 ITP patients for at least 6 months and 202 patients for at least 1 year.

Double-blind placebo-controlled studies

RAISE: 197 ITP patients were randomised 2:1, eltrombopag (n=135) to placebo (n=62), and randomisation was stratified based upon splenectomy status, use of ITP medicinal products at baseline and baseline platelet count. The dose of eltrombopag was adjusted during the 6 month treatment period based on individual platelet counts. All patients initiated treatment with eltrombopag 50 mg. From Day 29 to the end of treatment, 15 to 28 % of eltrombopag treated patients were maintained on ≤ 25 mg and 29 to 53 % received 75 mg.

In addition, patients could taper off concomitant ITP medicinal products and receive rescue treatments as dictated by local standard of care. More than half of all patients in each treatment group had ≥ 3 prior ITP therapies and 36 % had a prior splenectomy.

Median platelet counts at baseline were 16,000/µl for both treatment groups and in the eltrombopag group were maintained above 50,000/µl at all on-therapy visits starting at Day 15; in contrast, median platelet counts in the placebo group remained < 30,000/µl throughout the study.

Platelet count response between 50,000-400,000/µl in the absence of rescue treatment was achieved by significantly more patients in the eltrombopag treated group during the 6 month treatment period, $p < 0.001$. Fifty-four percent of the eltrombopag-treated patients and 13 % of placebo-treated patients achieved this level of response after 6 weeks of treatment. A similar platelet response was maintained throughout the study, with 52 % and 16 % of patients responding at the end of the 6-month treatment period.

Table 4: Secondary efficacy results from RAISE

	Eltrombopag N = 135	Placebo N = 62
Key secondary endpoints		
Number of cumulative weeks with platelet counts ≥ 50,000-400,000/µl, Mean (SD)	11.3 (9.46)	2.4 (5.95)
Patients with ≥ 75 % of assessments in the target range (50,000 to 400,000/µl), n (%)	51 (38)	4 (7)
P-value [a]	< 0.001	
Patients with bleeding (WHO Grades 1-4) at any time during 6 months, n (%)	106 (79)	56 (93)
P-value [a]	0.012	
Patients with bleeding (WHO Grades 2-4) at any time during 6 months, n (%)	44 (33)	32 (53)
P-value [a]	0.002	
Requiring rescue therapy, n (%)	24 (18)	25 (40)
P-value [a]	0.001	
Patients receiving ITP therapy at baseline (n)	63	31
Patients who attempted to reduce or discontinue baseline therapy, n (%)[b]	37 (59)	10 (32)
P value [a]	0.016	

a Logistic regression model adjusted for randomisation stratification variables

b 21 out of 63 (33 %) patients treated with eltrombopag who were taking an ITP medicinal product at baseline permanently discontinued all baseline ITP medicinal products.

At baseline, more than 70 % of ITP patients in each treatment group reported any bleeding (WHO Grades 1-4) and more than 20 % reported clinically significant bleeding (WHO Grades 2-4), respectively. The proportion of eltrombopag-treated patients with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced from baseline by approximately 50 % from Day 15 to the end of treatment throughout the 6 month treatment period.

TRA100773B: The primary efficacy endpoint was the proportion of responders, defined as ITP patients who had an increase in platelet counts to ≥ 50,000/µl at Day 43 from a baseline of < 30,000/µl; patients who withdrew prematurely due to a platelet count > 200,000/µl were considered responders, those that discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 patients with previously treated chronic ITP were randomised 2:1 eltrombopag (n = 76) to placebo (n = 38).

Table 5: Efficacy results from TRA100773B

	Eltrombopag N = 74	Placebo N = 38
Key primary endpoints		
Eligible for efficacy analysis, n	73	37
Patients with platelet count ≥ 50,000/µl after up to 42 days of dosing (compared to a baseline count of < 30,000/µl), n (%)	43 (59)	6 (16)
P value[a]	< 0.001	
Key secondary endpoints		
Patients with a Day 43 bleeding assessment, n	51	30
Bleeding (WHO Grades 1-4) n (%)	20 (39)	18 (60)
P value[a]	0.029	

a – Logistic regression model adjusted for randomisation stratification variables

In both RAISE and TRA100773B the response to eltrombopag relative to placebo was similar irrespective of ITP medicinal product use, splenectomy status and baseline platelet count (≤ 15,000/µl, > 15,000/µl) at randomisation.

In RAISE and TRA100773B studies, in the subgroup of ITP patients with baseline platelet count ≤ 15,000/µl the median platelet counts did not reach the target level (> 50,000/µl), although in both studies 43 % of these patients treated with eltrombopag responded after 6 weeks of treatment. In addition, in the RAISE study, 42 % of patients with baseline platelet count ≤ 15,000/µl treated with eltrombopag responded at the end of the 6 month treatment period. Forty-two to 60 % of the eltrombopag-treated patients in the RAISE study were receiving 75 mg from Day 29 to the end of treatment.

An open label, repeat dose study (3 cycles of 6 weeks of treatment, followed by 4 weeks off treatment) showed that episodic use with multiple courses of eltrombopag has demonstrated no loss of response.

Eltrombopag was administered to 299 ITP patients in an open-label extension study, 126 patients completed 1 year, 48 completed 18 months and 17 completed 2 years. The median baseline platelet count was 19,500/µl prior to eltrombopag administration. Median platelet counts at 12, 18 and 24 months on study were 68,000/µl, 75,000/µl and 119,000/µl, respectively.

Chronic hepatitis C associated thrombocytopenia studies

The efficacy and safety of eltrombopag for the treatment of thrombocytopenia in patients with HCV infection were evaluated in two randomized, double-blind, placebo-controlled studies. ENABLE 1 utilized peginterferon alfa-2a plus ribavirin for antiviral treatment and ENABLE 2 utilized peginterferon alfa-2b plus ribavirin. Patients did not receive direct acting antiviral agents. In both studies, patients with a platelet count of < 75,000/µl were enrolled and stratified by platelet count (< 50,000/µl and ≥ 50,000/µl to < 75,000/µl), screening HCV RNA (< 800,000 IU/ml and ≥ 800,000 IU/ml), and HCV genotype (genotype 2/3, and genotype 1/4/6).

Baseline disease characteristics were similar in both studies and were consistent with compensated cirrhotic HCV patient population. The majority of patients were HCV genotype 1 (64 %) and had bridging fibrosis/cirrhosis. Thirty-one percent of patients had been treated with prior HCV therapies, primarily pegylated interferon plus ribavirin. The median baseline platelet count was 59,500/µl in both treatment groups: 0.8 %, 28 % and 72 % of the patients recruited had platelet counts < 20,000/µl, < 50.000/µl and ≥ 50,000/µl respectively.

The studies consisted of two phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, subjects received open-label eltrombopag to increase the platelet count to ≥ 90,000/µl for ENABLE 1 and ≥ 100,000/µl for ENABLE 2. The median time to achieve the target platelet count ≥ 90,000/µl (ENABLE 1) or ≥ 100,000/µl (ENABLE 2) was 2 weeks.

The primary efficacy endpoint for both studies was sustained virologic response (SVR), defined as the percentage of patients with no detectable HCV-RNA at 24 weeks after completion of the planned treatment period.

In both HCV studies, a significantly greater proportion of patients treated with eltrombopag (n = 201, 21 %) achieved SVR compared to those treated with placebo (n=65, 13 %) (see Table 6). The improvement in the proportion of patients who achieved SVR was consistent across all subgroups in the randomisation strata (baseline platelet counts (< 50,000 vs. > 50,000), viral load (< 800,000 IU/ml vs. ≥ 800,000 IU/ml) and genotype (2/3 vs. 1/4/6)).

Table 6: Virologic response in HCV patients in ENABLE 1 and ENABLE 2

	Pooled Data		**ENABLE 1[a]**		**ENABLE 2[b]**	
Patients achieving target platelet counts & initiating antiviral therapy [c]	1439/1520 (95 %)		680/715 (95 %)		759/805 (94 %)	
	Eltrombopag	**Placebo**	**Eltrombopag**	**Placebo**	**Eltrombopag**	**Placebo**
Total number of patients entering Antiviral Treatment Phase	**n = 956**	**n = 485**	**n = 450**	**n = 232**	**n = 506**	**n = 253**
	% patients achieving virologic response					
Overall SVR [d]	21	13	23	14	19	13
HCV RNA Genotype						
Genotype 2/3	35	25	35	24	34	25
Genotype 1/4/6[e]	15	8	18	10	13	7
Albumin levels [f]						
≤ 35g/L	11	8				
> 35g/L	25	16				
MELD score[f]						
≥ 10	18	10				
< 10	23	17				

a Eltrombopag given in combination with peginterferon alfa-2a (180 mcg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1200 mg daily in 2 divided doses orally)

b Eltrombopag given in combination with peginterferon alfa-2b (1.5 mcg/kg once weekly for 48 weeks for genotype 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1400 mg orally in 2 divided doses)

c Target platelet count was ≥ 90,000/µl for ENABLE 1 and ≥ 100,000/µl for ENABLE 2. For ENABLE 1, 682 patients were randomised to the antiviral treatment phase; however 2 subjects then withdrew consent prior to receiving antiviral therapy.

d *P* value < 0.05 for eltrombopag versus placebo

e 64 % subjects participating in ENABLE 1 and ENABLE 2 were genotype 1

f Post-hoc analyses

Other secondary findings of the studies included the following; significantly fewer patients treated with eltrombopag prematurely discontinued antiviral therapy compared to placebo (45 % vs. 60 %, p = < 0.0001). A greater proportion of patients on eltrombopag did not require any antiviral dose reduction as compared to placebo (45 % versus 27 %). Eltrombopag treatment delayed and reduced the number of peginterferon dose reductions.

Severe Aplastic Anaemia

Eltrombopag was studied in a single-arm, single-centre open-label trial in 43 patients with severe aplastic anaemia with refractory thrombocytopenia following at least one prior immunosuppressive therapy (IST) and who had a platelet count ≤ 30,000/µl.

The majority of subjects, 33 (77%), were considered to have 'primary refractory disease', defined as having no prior adequate response to IST in any lineage. The remaining 10 subjects had insufficient platelet response to prior therapies. All 10 had received at least 2 prior IST regimens and 50% had received at least 3 prior IST regimens. Patients with diagnosis of Fanconi anemia, infection not responding to appropriate therapy, PNH clone size in neutrophils of ≥50%, where excluded from participation.

At baseline the median platelet count was 20,000/µl, haemoglobin was 8.4 g/dL, ANC was 0.58 x 10^9/L and absolute reticulocyte count was 24.3 x10^9/L. Eighty-six percent of patients were RBC transfusion dependent, and 91 % were platelet transfusion dependent. The majority of patients (84 %) had received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline.

The primary endpoint was haematological response assessed after 12 weeks of eltrombopag treatment. Haematological response was defined as meeting one or more of the following criteria: 1) platelet count increases to 20,000/µl above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) haemoglobin increase by > 1.5g/dL, or a reduction in ≥ 4 units of red blood cell (RBC) transfusions for 8 consecutive weeks; 3) absolute neutrophil count (ANC) increase of 100 % or an ANC increase > 0.5 x 10^9/L.

The haematological response rate was 40 % (17/43 patients; 95 % CI 25, 56), the majority were unilineage responses (13/17, 76%) whilst there were 3 bilineage and 1 trilineage responses at week 12. Eltrombopag was discontinued after 16 weeks if no haematological response or transfusion independence was observed. Patients who responded continued therapy in an extension phase of the study. A total of 14 patients entered the extension phase of the trial. Nine of these patients achieved a multi-lineage response, 4 of the 9 remain on treatment and 5 tapered off treatment with eltrombopag and maintained the response (median follow up: 20.6 months, range: 5.7 to 22.5 months). The remaining 5 patients discontinued treatment, three due to relapse at the month 3 extension visit.

During treatment with eltrombopag 59 % (23/39) became platelet transfusion independent (28 days without platelet transfusion) and 27 % (10/37) became RBC transfusion independent (56 days without RBC transfusion). The longest platelet transfusion free period for non-responders was 27 days (median). The longest platelet transfusion free period for responders was 287 days (median). The longest RBC transfusion free period for non-responders was 29 days (median). The longest RBC transfusion free period for responders was 266 days (median).

Over 50% of responders who were transfusion dependent at baseline, had >80% reduction in both platelet and RBC transfusion requirements compared to baseline.

Preliminary results from a supportive study (Study ELT116826), an ongoing non-randomised, phase II, single-arm, open-label study in refractory SAA subjects, showed consistent results. Data are limited to 21 out of the planned 60 patients with haematological responses reported by 52% of patients at 6 months. Multilineage responses were reported by 45% of patients.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Revolade in one or more subsets of the paediatric population in chronic idiopathic thrombocytopenic purpura (ITP) and Secondary Thrombocytopenia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Pharmacokinetics

The plasma eltrombopag concentration-time data collected in 88 patients with ITP in Studies TRA100773A and TRA100773B were combined with data from 111 healthy adult subjects in a population PK analysis. Plasma eltrombopag $AUC_{(0-\tau)}$ and C_{max} estimates for ITP patients are presented (Table 7).

Table 7: Geometric mean (95 % confidence intervals) of steady-state plasma eltrombopag pharmacokinetic parameters in adults with ITP

Eltrombopag dose, once daily	N	$AUC_{(0-\tau)}$[a], µg.h/ml	C_{max}[a], µg/ml
30 mg	28	47 (39, 58)	3.78 (3.18, 4.49)
50 mg	34	108 (88, 134)	8.01 (6.73, 9.53)
75 mg	26	168 (143, 198)	12.7 (11.0, 14.5)

a - $AUC_{(0-\tau)}$ and Cmax based on population PK post-hoc estimates.

Plasma eltrombopag concentration-time data collected in 590 subjects with HCV enrolled in Phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from patients with HCV enrolled in the Phase II study TPL102357 and healthy adult subjects in a population PK analysis. Plasma eltrombopag C_{max} $AUC_{(0-\tau)}$ estimates for patients with HCV enrolled in the Phase 3 studies are presented for each dose studied in Table 8.

Table 8 Geometric mean (95 % CI) steady-state plasma eltrombopag pharmacokinetic parameters in patients with chronic HCV

Eltrombopag dose (once daily)	**N**	**$AUC_{(0-\tau)}$ (µg.h/ml)**	**C_{max} (µg/ml)**
25 mg	330	118 (109, 128)	6.40 (5.97, 6.86)
50 mg	119	166 (143, 192)	9.08 (7.96, 10.35)
75 mg	45	301 (250, 363)	16.71 (14.26, 19.58)
100 mg	96	354 (304, 411)	19.19 (16.81, 21.91)

Data presented as geometric mean (95 % CI).
$AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates at the highest dose in the data for each patient.

Absorption and bioavailability

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure (see section 4.2). The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52 %.

Distribution

Eltrombopag is highly bound to human plasma proteins (> 99.9 %), predominantly to albumin. Eltrombopag is a substrate for BCRP, but is not a substrate for P-glycoprotein or OATP1B1.

Biotransformation

Eltrombopag is primarily metabolized through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64 % of plasma radiocarbon $AUC_{0-\infty}$. Minor metabolites due to glucuronidation and oxidation were also detected. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for oxidative metabolism of eltrombopag. Uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 are responsible for glucuronidation, and bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathway.

Elimination

Absorbed eltrombopag is extensively metabolised. The predominant route of eltrombopag excretion is via faeces (59 %) with 31 % of the dose found in the urine as metabolites. Unchanged parent compound (eltrombopag) is not detected in urine. Unchanged eltrombopag excreted in faeces accounts for approximately 20 % of the dose. The plasma elimination half-life of eltrombopag is approximately 21-32 hours.

Pharmacokinetic interactions

Based on a human study with radiolabelled eltrombopag, glucuronidation plays a minor role in the metabolism of eltrombopag. Human liver microsome studies identified UGT1A1 and UGT1A3 as the enzymes responsible for eltrombopag glucuronidation. Eltrombopag was an inhibitor of a number of UGT enzymes *in vitro*. Clinically significant drug interactions involving glucuronidation are not anticipated due to limited contribution of individual UGT enzymes in the glucuronidation of eltrombopag.

Approximately 21 % of an eltrombopag dose could undergo oxidative metabolism. Human liver microsome studies identified CYP1A2 and CYP2C8 as the enzymes responsible for eltrombopag oxidation. Eltrombopag does not inhibit or induce CYP enzymes based on *in vitro* and *in vivo* data (see section 4.5).

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter and an inhibitor of the BCRP transporter and eltrombopag increased exposure of the OATP1B1 and BCRP substrate rosuvastatin in a clinical drug interaction study (see section 4.5). In clinical studies with eltrombopag, a dose reduction of statins by 50 % was recommended.

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc (see sections 4.2 and 4.5).

Administration of a single 50 mg dose of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag $AUC_{(0-\infty)}$ and C_{max}. Whereas, low-calcium food [< 50 mg calcium] did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see sections 4.2 and 4.5).

Special patient populations

Renal impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with renal impairment. Following administration of a single 50 mg-dose, the $AUC_{0-\infty}$ of eltrombopag was 32 % to 36 % lower in subjects with mild to moderate renal impairment, and 60 % lower in subjects with severe renal impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with renal impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or urine analysis (see section 4.2). The efficacy and safety of eltrombopag has not been established in subjects with both moderate to severe renal impairment and hepatic impairment.

Hepatic impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with hepatic impairment. Following the administration of a single 50 mg dose, the $AUC_{0-\infty}$ of eltrombopag was 41 % higher in subjects with mild hepatic impairment and 80 % to 93 % higher in subjects with moderate to severe hepatic impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with hepatic impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured.

The influence of hepatic impairment on the pharmacokinetics of eltrombopag following repeat administration was evaluated using a population pharmacokinetic analysis in 28 healthy adults and 714 patients with hepatic impairment (673 patients with HCV and 41 patients with chronic liver disease of other aetiology). Of the 714 patients, 642 were with mild hepatic impairment, 67 with moderate hepatic impairment, and 2 with severe hepatic impairment. Compared to healthy volunteers, patients with mild hepatic impairment had approximately 111 % (95 % CI: 45 % to 283 %) higher plasma eltrombopag $AUC_{(0-\tau)}$ values and patients with moderate hepatic impairment had approximately 183 % (95 % CI: 90 % to 459 %) higher plasma eltrombopag $AUC_{(0-\tau)}$ values.

Therefore, eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see sections 4.2 and 4.4). For patients with HCV initiate eltrombopag at a dose of 25 mg once daily (see section 4.2).

Race

The influence of East Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (31 East Asians) and 88 patients with ITP (18 East Asians). Based on estimates from the population pharmacokinetic analysis, East Asian (i.e. Japanese, Chinese, Taiwanese and Korean) ITP patients had approximately 87 % higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East Asian patients who were predominantly Caucasian, without adjustment for body weight differences (see section 4.2).

The influence of East Asian ethnicity (such as Chinese, Japanese, Taiwanese, Korean, and Thai) on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 635 patients with HCV (145 East Asians and 69 Southeast Asians). Based on estimates from the population pharmacokinetic analysis, East Asian patients had approximately 55 % higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to patients of other races who were predominantly Caucasian (see section 4.2).

Gender

The influence of gender on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (14 females) and 88 patients with ITP (57 females). Based on estimates from the population pharmacokinetic analysis, female ITP patients had approximately 50 % higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients, without adjustment for body weight differences.

The influence of gender on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 635 patients with HCV (260 females). Based on model estimate, female HCV patient had approximately 41 % higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients.

Age

The influence of age on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 28 healthy subjects, 673 patients with HCV, and 41 patients with chronic liver disease of other aetiology ranging from 19 to 74 years old. There are no PK data on the use of eltrombopag in patients ≥ 75 years. Based on model estimate, elderly (≥ 65 years) patients had approximately 41 % higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to younger patients (see section 4.2).

5.3 Preclinical safety data

Eltrombopag does not stimulate platelet production in mice, rats or dogs because of unique TPO receptor specificity. Therefore, data from these animals do not fully model potential adverse effects related to the pharmacology of eltrombopag in humans, including the reproduction and carcinogenicity studies.

Treatment-related cataracts were detected in rodents and were dose and time-dependent. At ≥ 6 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 6 weeks and rats after 28 weeks of dosing. At ≥ 4 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human exposure in HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing. Cataracts have not been observed in dogs after 52 weeks of dosing at 2 times the human clinical exposure in ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC).

Renal tubular toxicity was observed in studies of up to 14 days duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2 year oral carcinogenicity study in mice at doses of 25, 75 and 150 mg/kg/day. Effects were less severe at lower doses and were characterized by a spectrum of regenerative changes. The exposure at the lowest dose was 1.2 times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 0.6 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC. Renal effects were not observed in rats after 28 weeks or in dogs after 52 weeks at exposures 4 and 2 times the human clinical exposure in ITP patients at 75 mg/day and 2 times and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Hepatocyte degeneration and/or necrosis, often accompanied by increased serum liver enzymes, was observed in mice, rats and dogs at doses that were associated with morbidity and mortality or were poorly tolerated. No hepatic effects were observed after chronic dosing in rats (28 weeks) and in dogs (52 weeks) at 4 or 2 times the human clinical exposure in ITP patients at 75 mg/day and 2 times and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

At poorly tolerated doses in rats and dogs (> 10 times the human clinical exposure in ITP patients at 75 mg/day and> 4 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC), decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (rats only) were observed in short term studies. There were no effects of note on red cell mass or reticulocyte counts after dosing for up to 28 weeks in rats, 52 weeks in dogs and 2 years in mice or rats at maximally tolerated doses which were 2 to 4 times human clinical exposure in ITP patients at 75 mg/day and ≤ 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Endosteal hyperostosis was observed in a 28 week toxicity study in rats at a non-tolerated dose of 60 mg/kg/day (6 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). There were no bone changes observed in mice or rats after lifetime exposure (2 years) at 4 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two in vivo assays in rats (micronucleus and unscheduled DNA synthesis, 10 times the human clinical exposure in ITP patients at 75 mg/day and 7 times the human clinical exposure in HCV patients at 100 mg/day, based on C_{max}). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally positive (< 3-fold increase in mutation frequency). These *in vitro* and *in vivo* findings suggest that eltrombopag does not pose a genotoxic risk to humans.

Eltrombopag did not affect female fertility, early embryonic development or embryofoetal development in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure in ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Also there was no effect on embryofoetal development in rabbits at doses up to 150 mg/kg/day, the highest dose tested (0.3 to 0.5 times the human clinical exposure in ITP patients at 75 mg/day and HCV Patients at 100 mg/day, based on AUC). However, at a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) in rats, eltrombopag treatment was associated with embryo lethality (increased pre- and post-implantation loss), reduced foetal body weight and gravid uterine weight in the female fertility study and a low incidence of cervical ribs and reduced foetal body weight in the embryofoetal development study. Eltrombopag should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus (see section 4.6). Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). In the pre- and post-natal development study in rats, there were no undesirable effects on pregnancy, parturition or lactation of F_0 female rats at maternally non-toxic doses (10 and 20 mg/kg/day) and no effects on the growth, development, neurobehavioral or reproductive function of the offspring (F_1). Eltrombopag was detected in the plasma of all F_1 rat pups for the entire 22 hour sampling period following administration of medicinal product to the F_0 dams, suggesting that rat pup exposure to eltrombopag was likely via lactation.

In vitro studies with eltrombopag suggest a potential phototoxicity risk; however, in rodents there was no evidence of cutaneous phototoxicity (10 times the human clinical exposure in ITP patients at 75 mg/day and 5 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) or ocular phototoxicity (≥ 5 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Furthermore, a clinical pharmacology study in 36 subjects showed no evidence that photosensitivity was increased following administration of eltrombopag 75 mg. This was measured by delayed phototoxic index. Nevertheless, a potential risk of photoallergy cannot be ruled out since no specific preclinical study could be performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Magnesium stearate
Mannitol (E421)
Microcrystalline cellulose
Povidone (K30)
Sodium starch glycolate Type A

Tablet coating
Hypromellose
Macrogol 400
Polysorbate 80
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminum blisters (PA/Alu/PVC/Alu) in a carton containing 14 or 28 film-coated tablets and multipacks containing 84 (3 packs of 28) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/001
EU/1/10/612/002
EU/1/10/612/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 March 2010
Date of latest renewal: 15 January 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Revolade 50 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Round, biconvex, brown film-coated tablet debossed with ‘GS UFU’ and ‘50’ on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Revolade is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Revolade may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated.

Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy (see sections 4.4 and 5.1).

Revolade is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation (see section 5.1).

4.2 Posology and method of administration

Eltrombopag treatment should be initiated and remain under the supervision of a physician who is experienced in the treatment of haematological diseases or the management of chronic hepatitis C and its complications.

Posology

Eltrombopag dosing requirements must be individualised based on the patient’s platelet counts. The objective of treatment with eltrombopag should not be to normalise platelet counts.

In most patients, measurable elevations in platelet counts take 1-2 weeks (see section 5.1).

Chronic immune (idiopathic) thrombocytopenia

The lowest dose of eltrombopag to achieve and maintain a platelet count ≥ 50,000/µl should be used. Dose adjustments are based upon the platelet count response. Do not use eltrombopag to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting eltrombopag and decreased within 1 to 2 weeks after discontinuation.

The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2).

Monitoring and dose adjustment

After initiating eltrombopag, adjust the dose to achieve and maintain a platelet count ≥ 50,000/µl as necessary to reduce the risk for bleeding. Do not exceed a dose of 75 mg daily.

Clinical haematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dose regimen of eltrombopag modified based on platelet counts as outlined in Table 1. During therapy with eltrombopag full blood counts (FBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count (≥50,000/µl for at least 4 weeks) has been achieved. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter.

The lowest effective dosing regimen to maintain platelet counts should be used as clinically indicated.

Table 1 Dose adjustments of eltrombopag in ITP patients

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day.
≥ 50,000/µl to ≤ 150,000/µl	Use lowest dose of eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
> 150,000/µl to ≤ 250,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 250,000/µl	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 25 mg.

Eltrombopag can be administered in addition to other ITP medicinal products. The dose regimen of concomitant ITP medicinal products should be modified, as medically appropriate, to avoid excessive increases in platelet counts during therapy with eltrombopag.

Wait for at least 2 weeks to see the effect of any dose adjustment on the patient's platelet response prior to considering another dose adjustment.

The standard eltrombopag dose adjustment, either decrease or increase, would be 25 mg once daily. However, in a few patients a combination of different film-coated tablet strengths on different days may be required.

Discontinuation

Treatment with eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of eltrombopag therapy at 75 mg once daily.

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician. The reoccurrence of thrombocytopenia is possible upon discontinuation of treatment (see section 4.4).

Chronic hepatitis C (HCV) associated thrombocytopenia

When eltrombopag is given in combination with antivirals reference should be made to the full summary of product characteristics of the respective coadministered medicinal products for comprehensive details of relevant safety information or contraindications.

In clinical studies, platelet counts generally began to increase within 1 week of starting eltrombopag. The aim of treatment with eltrombopag should be to achieve the minimum level of platelet counts needed to initiate antiviral therapy, in adherence to clinical practice recommendations. During antiviral therapy, the aim of treatment should be to keep platelet counts at a level that prevents the risk of bleeding complications, normally around 50,000-75,000/µl. Platelet counts > 75,000/µl should be avoided. The lowest dose of eltrombopag needed to achieve the targets should be used. Dose adjustments are based upon the platelet count response.

Initial dose regimen

Eltrombopag should be initiated at a dose of 25 mg once daily. No dosage adjustment is necessary for HCV patients of East Asian ancestry or patients with mild hepatic impairment (see section 5.2).

Monitoring and dose adjustment

The dose of eltrombopag should be adjusted in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate anti-viral therapy. Platelet counts should be monitored every week prior to starting antiviral therapy. On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose adjustments should be avoided (see Table 2).

During antiviral therapy, the dose of eltrombopag should be adjusted as necessary to avoid dose reductions of peginterferon due to decreasing platelet counts that may put patients at risk of bleeding (see Table 2). Platelet counts should be monitored weekly during antiviral therapy until a stable platelet count is achieved, normally around 50,000-75,000/µl. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter. Dose reductions on the daily dose by 25 mg should be considered if platelet counts exceed the required target. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.

Do not exceed a dose of 100 mg eltrombopag once daily.

Table 2 Dose adjustments of eltrombopag in HCV patients during antiviral therapy

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 100 mg/day.
≥ 50,000/µl to ≤ 100,000/µl	Use lowest dose of eltrombopag as necessary to avoid dose reductions of peginterferon
> 100,000/µl to ≤ 150,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments♦.
> 150,000/µl	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 25 mg*.

* - For patients taking 25 mg eltrombopag once daily, consideration should be given to reinitiating dosing at 25 mg every other day.

♦ - On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose reductions should be avoided.

Discontinuation

If after 2 weeks of eltrombopag therapy at 100 mg the required platelet level to initiate antiviral therapy is not achieved, eltrombopag should be discontinued.

Eltrombopag treatment should be terminated when antiviral therapy is discontinued unless otherwise justified. Excessive platelet count responses or important liver test abnormalities also necessitate discontinuation.

Severe Aplastic Anaemia

Initial Dose Regimen

Initiate eltrombopag at a dose of 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2). The treatment should not be initiated when the patients have existing cytogenetic abnormalities of chromosome 7.

Monitoring and dose adjustment

Haematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting eltrombopag (see section 5.1). Adjust the dose of eltrombopag in 50 mg increments every 2 weeks as necessary to achieve the target platelet count ≥ 50,000/µl. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg. Do not exceed a dose of 150 mg daily. Monitor clinical haematology and liver tests regularly throughout therapy with eltrombopag and modify the dosage regimen of eltrombopag based on platelet counts as outlined in Table 3.

Table 3 Dose adjustments of eltrombopag in patients with severe aplastic anaemia

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg.
≥ 50,000/µl to ≤ 150,000/µl	Use lowest dose of eltrombopag to maintain platelet counts.
> 150,000/µl to ≤ 250,000/µl	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 250,000/µl	Stop eltrombopag; for at least one week. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 50 mg.

Tapering for tri-lineage (white blood cells, red blood cells, and platelets) responders

For patients who achieve tri-lineage response, including transfusion independence, lasting at least 8 weeks: the dose of eltrombopag may be reduced by 50 %.

If counts remain stable after 8 weeks at the reduced dose, then discontinue eltrombopag and monitor blood counts. If platelet counts drop to < 30,000/µl, haemoglobin to < 9 g/dL or ANC < 0.5 x 10^9/L, eltrombopag may be reinitiated at the previous effective dose.

Discontinuation

If no haematological response has occurred after 16 weeks of therapy with eltrombopag, discontinue therapy. If new cytogenetic abnormalities are detected, evaluate whether continuation of eltrombopag is appropriate (see sections 4.4 and 4.8). Excessive platelet count responses (as outlined in Table 3) or important liver test abnormalities also necessitate discontinuation of eltrombopag (see section 4.8).

Special populations

Renal impairment

No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis (see section 5.2).

Hepatic impairment

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see section 4.4).

If the use of eltrombopag is deemed necessary for ITP patients with hepatic impairment the starting dose must be 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment wait 3 weeks before increasing the dose.

No dose adjustment is required for thrombocytopenic patients with chronic HCV and mild hepatic impairment (Child-Pugh score ≤ 6). Chronic HCV patients and severe aplastic anaemia patients with hepatic impairment should initiate eltrombopag at a dose of 25 mg once daily (see section 5.2). After initiating the dose of eltrombopag in patients with hepatic impairment wait 2 weeks before increasing the dose.

There is an increased risk for adverse events, including hepatic decompensation and thromboembolic events, in thrombocytopenic patients with advanced chronic liver disease treated with eltrombopag, either in preparation for invasive procedure or in HCV patients undergoing antiviral therapy (see sections 4.4 and 4.8).

Elderly

There are limited data on the use of eltrombopag in ITP patients aged 65 years and older and no clinical experience in ITP patients aged over 85 years. In the clinical studies of eltrombopag, overall no clinically significant differences in safety of eltrombopag were observed between subjects aged at least 65 years and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see section 5.2).

There are limited data on the use of eltrombopag in HCV and SAA patients aged over 75 years. Caution should be exercised in these patients (see section 4.4).

East Asian patients

For patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), including those with hepatic impairment, eltrombopag should be initiated at a dose of 25 mg once daily (see section 5.2).

Patient platelet count should continue to be monitored and the standard criteria for further dose modification followed.

Paediatric population

The safety and efficacy of eltrombopag has not been established in children and adolescents (< 18 years). No data are available.

<u>Method of administration</u>

Oral use. Eltrombopag should be taken at least four hours before or after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminium, selenium and zinc) (see sections 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to eltrombopag or to any of the excipients, listed in section 6.1.

4.4 Special warnings and precautions for use

There is an increased risk for adverse reactions, including potentially fatal hepatic decompensation and thromboembolic events, in thrombocytopenic HCV patients with advanced chronic liver disease, as defined by low albumin levels ≤ 35 g/L or MELD score ≥ 10, when treated with eltrombopag in combination with interferon-based therapy. In addition, the benefits of treatment in terms of the proportion achieving sustained virological response (SVR) compared with placebo were modest in these patients (especially for those with baseline albumin ≤ 35g/L) compared with the group overall. Treatment with eltrombopag in these patients should be initiated only by physicians experienced in the management of advanced HCV, and only when the risks of thrombocytopenia or withholding antiviral therapy necessitate intervention. If treatment is considered clinically indicated, close monitoring of these patients is required.

Combination with direct acting antiviral agents

Safety and efficacy have not been established in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C infection.

Risk of hepatotoxicity

Eltrombopag administration can cause abnormal liver function. In the controlled clinical studies in chronic ITP with eltrombopag, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin were observed (see section 4.8).

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function. Across the 3 placebo-controlled studies in chronic ITP, 1 patient in the placebo group and 1 patient in the eltrombopag group experienced a Grade 4 liver test abnormality.

In 2 controlled clinical studies in patients with HCV, ALT or AST ≥ 3 x ULN was reported in 34 % and 38 % of the eltrombopag and placebo groups, respectively. Most patients receiving eltrombopag in combination with peginterferon / ribavirin therapy will experience indirect hyperbilirubinaemia. Overall, total bilirubin ≥ 1.5 x ULN was reported in 76 % and 50 % of the eltrombopag and placebo groups, respectively.

Serum ALT, AST and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinaemia. If bilirubin is elevated perform fractionation. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilise, or return to baseline levels. Eltrombopag should be discontinued if ALT levels increase (≥ 3X ULN in patients with normal liver function or ≥ 3X baseline in patients with pre-treatment elevations in transaminases) and are:

- progressive, or
- persistent for ≥ 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

Exercise caution when administering eltrombopag to patients with hepatic disease. In ITP and SAA patients use a lower starting dose of eltrombopag and monitor closely when administering to patients with hepatic impairment (see section 4.2).

Hepatic decompensation (use with interferon)

Hepatic decompensation in patients with chronic hepatitis C: Monitor patients with low albumin levels (≤ 35 g/L) or with Model for End Stage Liver Disease (MELD) score ≥ 10 at baseline.

Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently in the eltrombopag arm (11 %) than in the placebo arm (6 %). In patients with low albumin levels (≤ 35 g/L) or MELD score ≥ 10 at baseline, there was a three-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. In addition, the benefits of treatment in terms of the proportion achieving SVR compared with placebo were modest in these patients (especially for those with baseline albumin ≤ 35g/L) compared with the group overall. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. The respective interferon summary of product characteristics should be referenced for discontinuation criteria. Eltrombopag should be terminated if antiviral therapy is discontinued for hepatic decompensation.

Thrombotic/Thromboembolic complications

In controlled studies in thrombocytopenic patients with HCV receiving interferon-based therapy (n = 1439), 38 out of 955 subjects (4 %) treated with eltrombopag and 6 out of 484 subjects (1 %) in the placebo group experienced thromboembolic events (TEEs). Reported thrombotic/thromboembolic complications included both venous and arterial events. The majority of TEEs were non-serious and resolved by the end of the study. Portal vein thrombosis was the most common TEE in both treatment groups (2 % in patients treated with eltrombopag versus < 1 % for placebo). No specific temporal relationship between start of treatment and event of TEE were observed. Patients with low albumin levels (≤ 35 g/L) or MELD ≥ 10 had a twofold greater risk of TEEs than those with higher albumin levels; those aged ≥ 60 years had a 2-fold greater risk of TEEs compared to younger patients. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients should be closely monitored for signs and symptoms of TEE.

The risk of TEEs has been found to be increased in patients with chronic liver disease (CLD) treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures. Six of 143 (4 %) adult patients with CLD receiving eltrombopag experienced TEEs (all of the portal venous system) and two of 145 (1 %) subjects in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five of the 6 patients treated with eltrombopag experienced the thrombotic complication at a platelet count > 200,000/µl and within 30 days of the last dose of eltrombopag. Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures.

In eltrombopag clinical trials in ITP thromboembolic events were observed at low and normal platelet counts. Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism including but not limited to inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing eltrombopag treatment if the platelet count exceeds the target levels (see section 4.2). The risk-benefit balance should be considered in patients at risk of thromboembolic events (TEEs) of any aetiology.

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate, exercise caution when administering eltrombopag to patients with hepatic impairment (see sections 4.2 and 4.8).

Bleeding following discontinuation of eltrombopag

Thrombocytopenia is likely to reoccur in ITP patients upon discontinuation of treatment with eltrombopag. Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increase the bleeding risk and in some cases may lead to bleeding. This risk is increased if eltrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with eltrombopag is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support. Platelet counts must be monitored weekly for 4 weeks following discontinuation of eltrombopag.

In HCV clinical trials, a higher incidence of gastrointestinal bleeding, including serious and fatal cases, was reported following discontinuation of peginterferon, ribavirin, and eltrombopag. Following discontinuation of therapy, patients should be monitored for any signs or symptoms of gastrointestinal bleeding.

Bone marrow reticulin formation and risk of bone marrow fibrosis

Eltrombopag may increase the risk for development or progression of reticulin fibres within the bone marrow. The relevance of this finding, as with other thrombopoietin receptor (TPO-R) agonists, has not been established yet.

Prior to initiation of eltrombopag, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, full blood count (FBC) with white blood cell count (WBC) differential should be performed monthly. If immature or dysplastic cells are observed, peripheral blood smears should be examined for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), treatment with eltrombopag should be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

Progression of existing Myelodysplastic Syndrome (MDS)

TPO-R agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO-R is predominantly expressed on the surface of cells of the myeloid lineage. For TPO-R agonists there is a concern that they may stimulate the progression of existing haematopoietic malignancies such as MDS.

In clinical studies with a TPO-R agonist in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to acute myeloid leukaemia (AML) were reported.

The diagnosis of ITP or SAA in adults and elderly patients should be confirmed by the exclusion of other clinical entities presenting with thrombocytopenia, in particular the diagnosis of MDS must be excluded. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms, or abnormal signs such as increased peripheral blast cells.

The effectiveness and safety of eltrombopag have not been established for use in other thrombocytopenic conditions including chemotherapy-induced thrombocytopenia or MDS. Eltrombopag should not be used outside of clinical trials for the treatment of thrombocytopenia due to MDS or any other cause of thrombocytopenia other than the approved indications.

Cytogenetic abnormalities and progression to MDS/AML in patients with SAA:

Cytogenetic abnormalities are known to occur in SAA patients. It is not known whether eltrombopag increases the risk of cytogenetic abnormalities in patients with SAA. In the phase II SAA clinical study with eltrombopag, the incidence of new cytogenetic abnormalities was observed in 19% of patients [8/43 (where 5 of them had changes in chromosome 7)]. The median time on study to a cytogenetic abnormality was 2.9 months.

In clinical trials with eltrombopag in SAA, 4% of patients (5/133) were diagnosed with MDS. The median time to diagnosis was 3 months from the start of eltrombopag treatment.

For SAA patients refractory to or heavily pretreated with prior immunosuppressive therapy, bone marrow examination with aspirations for cytogenetics is recommended prior to initiation of eltrombopag, at 3 months of treatment and 6 months thereafter. If new cytogenetic abnormalities are detected, evaluate whether continuation of eltrombopag is appropriate.

Ocular changes

Cataracts were observed in toxicology studies of eltrombopag in rodents (see section 5.3). In controlled studies in thrombocytopenic patients with HCV receiving interferon therapy (n = 1439), progression of pre-existing baseline cataract(s) or incident cataracts was reported in 8 % of the eltrombopag group and 5 % of the placebo group. Retinal haemorrhages, mostly Grade 1 or 2, have been reported in HCV patients receiving interferon, ribavirin and eltrombopag (2 % of the eltrombopag group and 2 % of the placebo group. Haemorrhages occurred on the surface of the retina (preretinal), under the retina (subretinal), or within the retinal tissue. Routine ophthalmologic monitoring of patients is recommended.

QT/QTc prolongation

A QTc study in healthy volunteers dosed 150 mg eltrombopag per day did not show a clinically significant effect on cardiac repolarisation. QTc interval prolongation has been reported in clinical trials of patients with ITP and thrombocytopenic patients with HCV. The clinical significance of these QTc prolongation events is unknown.

Loss of response to eltrombopag

A loss of response or failure to maintain a platelet response with eltrombopag treatment within the recommended dosing range should prompt a search for causative factors, including an increased bone marrow reticulin.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of eltrombopag on other medicinal products

HMG CoA reductase inhibitors

In vitro studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter. *In vitro* studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor. Administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin C_{max} 103 % (90 % confidence interval [CI]: 82 %, 126 %) and $AUC_{0-\infty}$ 55 % (90 % CI: 42 %, 69 %). Interactions are also expected with other HMG-CoA reductase inhibitors, including atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin. When co-administered with eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken (see section 5.2).

OATP1B1 and BCRP substrates

Concomitant administration of eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should be undertaken with caution (see section 5.2).

Cytochrome P450 substrates

In studies utilizing human liver microsomes, eltrombopag (up to 100 μM) showed no *in vitro* inhibition of the CYP450 enzymes 1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11 and was an inhibitor of CYP2C8 and CYP2C9 as measured using paclitaxel and diclofenac as the probe substrates. Administration of eltrombopag 75 mg once daily for 7 days to 24 healthy male subjects did not inhibit or induce the metabolism of probe substrates for 1A2 (caffeine), 2C19 (omeprazole), 2C9 (flurbiprofen), or 3A4 (midazolam) in humans. No clinically significant interactions are expected when eltrombopag and CYP450 substrates are co-administered (see section 5.2).

HCV Protease Inhibitors

Dose adjustment is not required when eltrombopag is co-administered with either telaprevir or boceprevir. Co-administration of a single dose of eltrombopag 200 mg with telaprevir 750 mg Q8h did not alter plasma telaprevir exposure.

Co-administration of a single dose of eltrombopag 200 mg with boceprevir 800 mg Q8h did not alter plasma boceprevir $AUC_{(0-\tau)}$, but increased C_{max} by 20 %, and decreased C_{min} by 32 %. The clinical relevance of the decrease in C_{min} has not been established, increased clinical and laboratory monitoring for HCV suppression is recommended.

Effects of other medicinal products on eltrombopag

Polyvalent cations (chelation)

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc. Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-\infty}$ by 70 % (90 % CI: 64 %, 76 %) and C_{max} by 70 % (90 % CI: 62 %, 76 %). Antacids, dairy products and other products containing polyvalent cations, such as mineral supplements, must be administered at least four hours apart from eltrombopag dosing to avoid significant reduction in eltrombopag absorption due to chelation (see sections 4.2 and 5.2).

Food interaction

Administration of a single 50 mg-dose of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag $AUC_{0-\infty}$ by 59 % (90 % CI: 54 %, 64 %) and C_{max} by 65 % (90 % CI: 59 %, 70 %). Food low in calcium [< 50 mg calcium] including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see sections 4.2 and 5.2.).

Lopinavir/ritonavir

Co-administration of eltrombopag with lopinavir/ritonavir (LPV/RTV) may cause a decrease in the concentration of eltrombopag. A study in 40 healthy volunteers showed that the co-administration of single dose eltrombopag 100 mg with repeat dose LPV/RTV 400 /100 mg twice daily resulted in a reduction in eltrombopag plasma $AUC_{(0-\infty)}$ by 17 % (90 % CI: 6.6 %, 26.6 %). Therefore, caution should be used when co-administration of eltrombopag with LPV/RTV takes place. Platelet count should be closely monitored in order to ensure appropriate medical management of the dose of eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued.

CYP1A2 and CYP2C8 inhibitors and inducers

Eltrombopag is metabolized through multiple pathways including CYP1A2, CYP2C8, UGT1A1, and UGT1A3 (see section 5.2). Medicinal products that inhibit or induce a single enzyme are unlikely to significantly affect plasma eltrombopag concentrations; whereas medicinal products that inhibit or induce multiple enzymes have the potential to increase (e.g. fluvoxamine) or decrease (e.g. rifampicin) eltrombopag concentrations.

HCV Protease Inhibitors

Results of a drug-drug pharmacokinetic (PK) interaction study show that co-administration of repeat doses of boceprevir 800 mg Q8h or telaprevir 750 mg Q8h with a single dose of eltrombopag 200 mg did not alter plasma eltrombopag exposure to a clinically significant extent.

Medicinal products for treatment of ITP

Medicinal products used in the treatment of ITP in combination with eltrombopag in clinical studies included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Platelet counts should be monitored when combining eltrombopag with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of eltrombopag in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Revolade is not recommended during pregnancy.

Women of childbearing potential / Contraception in males and females

Revolade is not recommended in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether eltrombopag/metabolites are excreted in human milk. Studies in animals have shown that eltrombopag is likely secreted into milk (see section 5.3); therefore a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to continue/abstain from Revolade therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Fertility was not affected in male or female rats at exposures that were comparable to those in humans. However a risk for humans cannot be ruled out (see section 5.3).

4.7 Effects on ability to drive and use machines

Eltrombopag has negligible influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of eltrombopag, including dizziness and lack of alertness, should be borne in mind when considering the patient's ability to perform tasks that require judgment, motor and cognitive skills.

4.8 Undesirable effects

Summary of the safety profile

Based on an analysis of all chronic ITP patients receiving eltrombopag in 4 controlled and 2 uncontrolled clinical studies, the overall incidence of adverse reactions in subjects treated with eltrombopag was 79 % (433/530). The mean duration of exposure to eltrombopag was 260 days and patient year's exposure was 390 in this study population.

ENABLE 1 (TPL103922 N=716) and ENABLE 2 (TPL108390 N=805) were randomized, double-blind, placebo-controlled, multicentre studies to assess the efficacy and safety of eltrombopag in thrombocytopenic subjects with HCV infection who were otherwise eligible to initiate antiviral therapy with interferon and ribavirin therapy.

In the HCV studies the safety population consisted of all randomized subjects who received double-blind study drug during Part 2 of ENABLE 1 (eltrombopag treatment N=449, placebo N=232) and ENABLE 2 (eltrombopag treatment N=506, placebo N=252). Subjects are analysed according to the treatment received (total safety double blind population, eltrombopag N=955 and placebo N=484).

The safety of eltrombopag in severe aplastic anaemia was assessed in a single-arm, open-label trial (N=43) in which 12 patients (28 %) were treated for > 6 months and 9 patients (21 %) were treated for > 1 year.

The most important serious adverse reactions identified in the ITP or HCV trials were hepatotoxicity and thrombotic/thromboembolic events.

The most common adverse reactions (experienced by at least 10 % of patients) of any grade in the ITP or HCV trials included; headache, anaemia, decreased appetite, insomnia, cough, nausea, diarrhoea, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza like illness, asthenia, chills and peripheral oedema.

List of adverse reactions

The adverse reactions in the ITP studies (N = 550), the HCV studies (N = 955), the SAA studies (N = 43) and post-marketing reports are listed below by MedDRA system organ class and by frequency.

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1,000 to < 1/100)
Rare	(≥ 1/10,000 to < 1/1,000)
Very rare	(< 1/10,000)
Not known	(cannot be estimated from the available data)

ITP study population

Infections and infestations

Uncommon Pharyngitis, Urinary tract infection, Influenza, Oral herpes, Pneumonia, Sinusitis, Tonsillitis, Respiratory tract infection, Gingivitis, Skin infection

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Uncommon Rectosigmoid cancer

Blood and lymphatic system disorders

Uncommon Anaemia, Anisocytosis, Eosinophilia, Haemolytic anaemia, Leukocytosis, Myelocytosis, Thrombocytopenia, Haemoglobin increased, Band neutrophil count increased, Haemoglobin decreased, Myelocyte present, Platelet count increased, White blood cell count decreased

Immune system disorders

Uncommon Hypersensitivity

Metabolism and nutrition disorders

Uncommon Anorexia, Hypokalaemia, Decreased appetite, Gout, Hypocalcaemia, Blood uric acid increased

Psychiatric disorders

Uncommon Sleep disorder, Depression, Apathy, Mood altered, Tearfulness

Nervous systems disorders

Common Paraesthesia

Uncommon Hypoaesthesia, Somnolence, Migraine, Tremor, Balance disorder, Dysaesthesia, Hemiparesis, Migraine with aura, Neuropathy peripheral, Peripheral sensory neuropathy, Speech disorder, Toxic neuropathy, Vascular headache

Eye disorders

Common Dry eye

Uncommon Vision blurred, Lenticular opacities, Astigmatism, Cataract cortical, Eye pain, Lacrimation increased, Retinal haemorrhage, Retinal pigment epitheliopathy, Visual acuity reduced, Visual impairment, Visual acuity tests abnormal, Blepharitis and Keratoconjunctivitis sicca

Ear and labyrinth disorders

Uncommon Ear pain, Vertigo

Cardiac disorders

Uncommon Tachycardia, Acute myocardial infarction, Cardiovascular disorder, Cyanosis, Sinus tachycardia, Electrocardiogram QT prolonged

Vascular disorders

Uncommon Deep vein thrombosis, Embolism, Hot flush, Thrombophlebitis superficial, Flushing, Haematoma

Respiratory, thoracic and mediastinal disorders

Uncommon Pulmonary embolism, Pulmonary infarction, Nasal discomfort, Oropharyngeal blistering, Oropharyngeal pain, Sinus disorder, Sleep apnoea syndrome

Gastrointestinal disorders

Common Nausea, Diarrhoea, Mouth ulceration

Uncommon Dry mouth, Vomiting, Abdominal pain, Glossodynia, Mouth haemorrhage, Abdominal tenderness, Faeces discoloured, Flatulence, Food poisoning, Frequent bowel movements, Haematemesis, Oral discomfort

Hepatobiliary disorders

Common Alanine aminotransferase increased*, Aspartate aminotransferase increased*, Hyperbilirubinaemia, Hepatic function abnormal

Uncommon Cholestasis, Hepatic lesion, Hepatitis

*Increase of alanine aminotransferase and aspartate aminotransferase may occur simultaneously, although at a lower frequency.

Skin and subcutaneous tissue disorders

Common Rash, Alopecia

Uncommon Hyperhidrosis, Pruritus generalised, Urticaria, Dermatosis, Petechiae, Cold sweat, Erythema, Melanosis, Pigmentation disorder, Skin discolouration, Skin exfoliation

Musculoskeletal and connective tissue disorders

Common Myalgia, Muscle spasm, Musculosketal pain, Bone pain, Back pain

Uncommon Muscular weakness

Renal and urinary disorders

Uncommon Renal failure, Leukocyturia, Lupus nephritis, Nocturia, Proteinuria, Blood urea increased, Blood creatinine increased, Urine protein/creatinine ratio increased

Reproductive system and breast disorders

Common Menorrhagia

General disorders and administration site conditions

Uncommon Chest pain, Feeling hot, Vessel puncture site haemorrhage, Asthenia, Feeling jittery, Inflammation of wound, Malaise, Pyrexia, Sensation of foreign body

Investigations

Uncommon Blood albumin increased, Blood alkaline phosphatase increased, Protein total increased, Blood albumin decreased, pH urine increased

Injury, poisoning and procedural complications

Uncommon Sunburn

HCV study population (in combination with anti-viral interferon and ribavirin therapy)

Infections and infestations

Common Urinary tract infection, Upper respiratory tract infection, Bronchitis, Nasopharyngitis, Influenza, Oral herpes, Gastroenteritis, Pharyngitis

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Common Hepatic neoplasm malignant

Blood and lymphatic system disorders

Very common Anaemia
Common Lymphopenia, Haemolytic anaemia

Metabolism and nutrition disorders

Very common Decreased appetite
Common Hyperglycaemia, Abnormal loss of weight

Psychiatric disorders

Very common Insomnia
Common Depression, Anxiety, Sleep disorder, Confusional state, Agitation

Nervous systems disorders

Very common Headache
Common Dizziness, Disturbance in attention, Dysgeusia, Hepatic encephalopathy, Lethargy, Memory impairment, Paraesthesia

Eye disorders

Common Cataract, Retinal exudates, Dry Eye, Ocular icterus, Retinal haemorrhage

Ear and labyrinth disorders

Common Vertigo

Cardiac disorders

Common Palpitations

Respiratory, thoracic and mediastinal disorders

Very common Cough
Common Dyspnoea, Oropharyngeal pain, Dyspnoea exertional, Productive cough

Gastrointestinal disorders

Very common Nausea, Diarrhoea
Common Vomiting, Ascites, Abdominal pain, Abdominal pain upper, Dyspepsia, Dry mouth, Constipation, Abdominal distension, Toothache, Stomatitis, Gastrooesophagal reflux disease, Haemorrhoids, Abdominal discomfort, Gastritis, Varices oesophageal, Aphthous stomatitis, Oesophageal varices haemorrhage

Hepatobiliary disorders

Common Hyperbilirubinaemia, Jaundice, Portal vein thrombosis, Hepatic failure

Skin and subcutaneous tissue disorders

Very common Pruritus, Alopecia
Common Rash, Dry skin, Eczema, Rash pruritic, Erythema, Hyperhidrosis, Pruritus generalised, Night sweats, Skin lesion

Musculoskeletal and connective tissue disorder

Very common Myalgia
Common Arthralgia, Muscle spasms, Back pain, Pain in extremity, Musculoskeletal pain, Bone pain

Renal and urinary disorders

Uncommon Dysuria

General disorders and administration site conditions

Very common Pyrexia, Fatigue, Influenza like illness, Asthenia, Chills, Oedema peripheral
Common Irritability, Pain, Malaise, Injection site reaction, Non-cardiac chest pain, Oedema, Injection site rash, Chest discomfort, Injection site pruritus

Investigations

Common Blood bilirubin increased, Weight decreased, White blood cell count decreased, Haemoglobin decreased, Neutrophil count decreased, International normalised ratio increased, Activated partial thromboplastin time prolonged, Blood glucose increased, Blood albumin decreased, Electrocardiogram QT prolonged

SAA study population

Blood and lymphatic system disorders

Common Neutropenia, Splenic infarction

Metabolism and nutrition disorders

Common Iron overload, Decreased appetite, Hypoglycaemia, Increased appetite

Psychiatric disorders

Very common Insomnia

Common Anxiety, Depression

Nervous systems disorders

Very common Headache, Dizziness

Common Syncope

Eye disorders

Common Dry eye, Eye pruritus, Cataract, Ocular icterus, Vision blurred, Visual impairment, Vitreous floaters

Respiratory, thoracic and mediastinal disorders

Very common Cough. Dyspnoea, Oropharyngeal Pain, Rhinorrhoea

Common Epistaxis

Gastrointestinal disorders

Very common Abdominal pain, Diarrhoea, Nausea

Common Gingival bleeding, Oral mucosal blistering, Oral pain, Vomiting, Abdominal discomfort, Abdominal pain, Constipation, Abdominal distension, Dysphagia, Faeces discoloured, Swollen tongue, Gastrointestinal motility disorder, Flatulence

Hepatobiliary disorders

Very common Transaminases increased

Common Blood bilirubin increased (hyperbilirubinemia), Jaundice

Skin and subcutaneous tissue disorders

Very common	Ecchymosis
Common	Petechiae, Rash, Pruritus, Urticaria, Skin lesion, Rash Macular

Musculosketal and connective tissue disorders

Very common	Arthralgia, Muscle spasms, Pain in extremity
Common	Back pain, Myalgia, Bone pain

Renal and urinary disorders

Common	Chromaturia

General disorders and administration site conditions

Very common	Fatigue, Febrile neutropenia, Pyrexia
Common	Asthenia, Oedema peripheral, Chills, Malaise

Investigations

Common	Blood creatine phosphokinase increased

Description of selected adverse reactions

Thrombotic/Thromboembolic events (TEEs)

In 3 controlled and 2 uncontrolled clinical studies, among adult chronic ITP patients receiving eltrombopag (n = 446), 17 subjects experienced a total of 19 TEEs, which included (in descending order of occurrence) deep vein thrombosis (n = 6), pulmonary embolism (n = 6), acute myocardial infarction (n = 2), cerebral infarction (n = 2), embolism (n = 1) (see section 4.4).

In a placebo-controlled study (n = 288, Safety population), following 2 weeks treatment in preparation for invasive procedures, 6 of 143 (4 %) adult patients with chronic liver disease receiving eltrombopag experienced 7 TEEs of the portal venous system and 2 of 145 (1 %) subjects in the placebo group experienced 3 TEEs. Five of the 6 patients treated with eltrombopag experienced the TEE at a platelet count > 200,000/µl.

No specific risk factors were identified in those subjects who experienced a TEE with the exception of platelet counts ≥ 200,000/µl (see section 4.4).

In controlled studies in thrombocytopenic patients with HCV (n = 1439), 38 out of 955 subjects (4 %) treated with eltrombopag experienced a TEE and 6 out of 484 subjects (1 %) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (2 % in patients treated with eltrombopag versus < 1 % for placebo) (see section 4.4). Patients with low albumin levels (≤ 35 g/L) or MELD ≥ 10 had a twofold greater risk of TEEs than those with higher albumin levels; those aged ≥ 60 years had a 2-fold greater risk of TEEs compared to younger patients.

Hepatic decompensation (use with interferon)

Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently in the eltrombopag arm (11 %) than in the placebo arm (6 %). In patients with low albumin levels (≤ 35 g/L) or Model for End-Stage Liver Disease (MELD) score ≥ 10 at baseline, there was a three-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation (see section 4.4).

Thrombocytopenia following discontinuation of treatment

In the 3 controlled clinical ITP studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8 % and 8 % of the eltrombopag and placebo groups, respectively (see section 4.4).

Increased bone marrow reticulin

Across the programme, no patients had evidence of clinically relevant bone marrow abnormalities or clinical findings that would indicate bone marrow dysfunction. In one ITP patient, eltrombopag treatment was discontinued due to bone marrow reticulin (see section 4.4).

Cytogenetic abnormalities

In the single-arm, open-label trial in SAA, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight (19%) patients had a new cytogenetic abnormality reported, including 5 patients who had changes in chromosome 7. In the two ongoing studies (ELT116826 and ELT116643), cytogenetic abnormalities have been detected in 4/28 (14%) and 4/62 (6%) subjects in each study.

Haematologic malignancies

In the single-arm, open label trial in SAA, three (7%) patients were diagnosed with MDS following treatment with eltrombopag, in the two ongoing studies (ELT116826 and ELT116643), 1/28 (4%) and 1/62 (2%) subject has been diagnosed with MDS or AML in each study.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, consider oral administration of a metal cation-containing preparation, such as calcium, aluminium, or magnesium preparations to chelate eltrombopag and thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with eltrombopag in accordance with dosing and administration recommendations (see section 4.2).

In the clinical studies there was one report of overdose where the subject ingested 5000 mg of eltrombopag. Reported adverse reactions included mild rash, transient bradycardia, ALT and AST elevation, and fatigue. Liver enzymes measured between Days 2 and 18 after ingestion peaked at a 1.6-fold ULN in AST, a 3.9-fold ULN in ALT, and a 2.4-fold ULN in total bilirubin, The platelet counts were 672,000/µl on day 18 after ingestion and the maximum platelet count was 929,000/µl. All events were resolved without sequelae following treatment.

Because eltrombopag is not significantly renally excreted and is highly bound to plasma proteins, haemodialysis would not be expected to be an effective method to enhance the elimination of eltrombopag.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, other systemic hemostatics. ATC code: B02BX 05.

Mechanism of action

TPO is the main cytokine involved in regulation of megakaryopoiesis and platelet production, and is the endogenous ligand for the TPO-R. Eltrombopag interacts with the transmembrane domain of the human TPO-R and initiates signalling cascades similar but not identical to that of endogenous thrombopoietin (TPO), inducing proliferation and differentiation from bone marrow progenitor cells.

Clinical efficacy and safety

Chronic immune (idiopathic) thrombocytopenia (ITP) studies
Two Phase III, randomised, double-blind, placebo-controlled studies RAISE (TRA102537) and TRA100773B and two open-label studies REPEAT (TRA108057) and EXTEND (TRA105325) evaluated the safety and efficacy of eltrombopag in adult patients with previously treated chronic ITP. Overall, eltrombopag was administered to 277 ITP patients for at least 6 months and 202 patients for at least 1 year.

Double-blind placebo-controlled studies

RAISE: 197 ITP patients were randomised 2:1, eltrombopag (n=135) to placebo (n=62), and randomisation was stratified based upon splenectomy status, use of ITP medicinal products at baseline and baseline platelet count. The dose of eltrombopag was adjusted during the 6 month treatment period based on individual platelet counts. All patients initiated treatment with eltrombopag 50 mg. From Day 29 to the end of treatment, 15 to 28 % of eltrombopag treated patients were maintained on ≤ 25 mg and 29 to 53 % received 75 mg.

In addition, patients could taper off concomitant ITP medicinal products and receive rescue treatments as dictated by local standard of care. More than half of all patients in each treatment group had ≥ 3 prior ITP therapies and 36 % had a prior splenectomy.

Median platelet counts at baseline were 16,000/µl for both treatment groups and in the eltrombopag group were maintained above 50,000/µl at all on-therapy visits starting at Day 15; in contrast, median platelet counts in the placebo group remained < 30,000/µl throughout the study.

Platelet count response between 50,000-400,000/µl in the absence of rescue treatment was achieved by significantly more patients in the eltrombopag treated group during the 6 month treatment period, $p < 0.001$. Fifty-four percent of the eltrombopag-treated patients and 13 % of placebo-treated patients achieved this level of response after 6 weeks of treatment. A similar platelet response was maintained throughout the study, with 52 % and 16 % of patients responding at the end of the 6-month treatment period.

Table 4: Secondary efficacy results from RAISE

	Eltrombopag N = 135	Placebo N = 62
Key secondary endpoints		
Number of cumulative weeks with platelet counts ≥ 50,000-400,000/µl, Mean (SD)	11.3 (9.46)	2.4 (5.95)
Patients with ≥ 75 % of assessments in the target range (50,000 to 400,000/µl), n (%)	51 (38)	4 (7)
P-value [a]	< 0.001	
Patients with bleeding (WHO Grades 1-4) at any time during 6 months, n (%)	106 (79)	56 (93)
P-value [a]	0.012	
Patients with bleeding (WHO Grades 2-4) at any time during 6 months, n (%)	44 (33)	32 (53)
P-value [a]	0.002	
Requiring rescue therapy, n (%)	24 (18)	25 (40)
P-value [a]	0.001	
Patients receiving ITP therapy at baseline (n)	63	31
Patients who attempted to reduce or discontinue baseline therapy, n (%)[b]	37 (59)	10 (32)
P value [a]	0.016	

a Logistic regression model adjusted for randomisation stratification variables

b 21 out of 63 (33 %) patients treated with eltrombopag who were taking an ITP medicinal product at baseline permanently discontinued all baseline ITP medicinal products.

At baseline, more than 70 % of ITP patients in each treatment group reported any bleeding (WHO Grades 1-4) and more than 20 % reported clinically significant bleeding (WHO Grades 2-4), respectively. The proportion of eltrombopag-treated patients with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced from baseline by approximately 50 % from Day 15 to the end of treatment throughout the 6 month treatment period.

TRA100773B: The primary efficacy endpoint was the proportion of responders, defined as ITP patients who had an increase in platelet counts to ≥ 50,000/µl at Day 43 from a baseline of < 30,000/µl; patients who withdrew prematurely due to a platelet count > 200,000/µl were considered responders, those that discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 patients with previously treated chronic ITP were randomised 2:1 eltrombopag (n = 76) to placebo (n = 38).

Table 5: Efficacy results from TRA100773B

	Eltrombopag N = 74	Placebo N = 38
Key primary endpoints		
Eligible for efficacy analysis, n	73	37
Patients with platelet count ≥ 50,000/µl after up to 42 days of dosing (compared to a baseline count of < 30,000/µl), n (%)	43 (59)	6 (16)
P value[a]	< 0.001	
Key secondary endpoints		
Patients with a Day 43 bleeding assessment, n	51	30
Bleeding (WHO Grades 1-4) n (%)	20 (39)	18 (60)
P value[a]	0.029	

a – Logistic regression model adjusted for randomisation stratification variables

In both RAISE and TRA100773B the response to eltrombopag relative to placebo was similar irrespective of ITP medicinal product use, splenectomy status and baseline platelet count (≤ 15,000/µl, > 15,000/µl) at randomisation.

In RAISE and TRA100773B studies, in the subgroup of ITP patients with baseline platelet count ≤ 15,000/µl the median platelet counts did not reach the target level (> 50,000/µl), although in both studies 43 % of these patients treated with eltrombopag responded after 6 weeks of treatment. In addition, in the RAISE study, 42 % of patients with baseline platelet count ≤ 15,000/µl treated with eltrombopag responded at the end of the 6 month treatment period. Forty-two to 60 % of the eltrombopag-treated patients in the RAISE study were receiving 75 mg from Day 29 to the end of treatment.

An open label, repeat dose study (3 cycles of 6 weeks of treatment, followed by 4 weeks off treatment) showed that episodic use with multiple courses of eltrombopag has demonstrated no loss of response.

Eltrombopag was administered to 299 ITP patients in an open-label extension study, 126 patients completed 1 year, 48 completed 18 months and 17 completed 2 years. The median baseline platelet count was 19,500/µl prior to eltrombopag administration. Median platelet counts at 12, 18 and 24 months on study were 68,000/µl, 75,000/µl and 119,000/µl, respectively.

Chronic hepatitis C associated thrombocytopenia studies

The efficacy and safety of eltrombopag for the treatment of thrombocytopenia in patients with HCV infection were evaluated in two randomized, double-blind, placebo-controlled studies. ENABLE 1 utilized peginterferon alfa-2a plus ribavirin for antiviral treatment and ENABLE 2 utilized peginterferon alfa-2b plus ribavirin. Patients did not receive direct acting antiviral agents. In both studies, patients with a platelet count of < 75,000/µl were enrolled and stratified by platelet count (< 50,000/µl and ≥ 50,000/µl to < 75,000/µl), screening HCV RNA (< 800,000 IU/ml and ≥ 800,000 IU/ml), and HCV genotype (genotype 2/3, and genotype 1/4/6).

Baseline disease characteristics were similar in both studies and were consistent with compensated cirrhotic HCV patient population. The majority of patients were HCV genotype 1 (64 %) and had bridging fibrosis/cirrhosis. Thirty-one percent of patients had been treated with prior HCV therapies, primarily pegylated interferon plus ribavirin. The median baseline platelet count was 59,500/µl in both treatment groups: 0.8 %, 28 % and 72 % of the patients recruited had platelet counts < 20,000/µl, < 50.000/µl and ≥ 50,000/µl respectively.

The studies consisted of two phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, subjects received open-label eltrombopag to increase the platelet count to ≥ 90,000/µl for ENABLE 1 and ≥ 100,000/µl for ENABLE 2. The median time to achieve the target platelet count ≥ 90,000/µl (ENABLE 1) or ≥ 100,000/µl (ENABLE 2) was 2 weeks.

The primary efficacy endpoint for both studies was sustained virologic response (SVR), defined as the percentage of patients with no detectable HCV-RNA at 24 weeks after completion of the planned treatment period.

In both HCV studies, a significantly greater proportion of patients treated with eltrombopag (n = 201, 21 %) achieved SVR compared to those treated with placebo (n=65, 13 %) (see Table 6). The improvement in the proportion of patients who achieved SVR was consistent across all subgroups in the randomisation strata (baseline platelet counts (< 50,000 vs. > 50,000), viral load (< 800,000 IU/ml vs. ≥ 800,000 IU/ml) and genotype (2/3 vs. 1/4/6)).

Table 6: Virologic response in HCV patients in ENABLE 1 and ENABLE 2

	Pooled Data		**ENABLE 1[a]**		**ENABLE 2[b]**	
Patients achieving target platelet counts & initiating antiviral therapy [c]	1439/1520 (95 %)		680/715 (95 %)		759/805 (94 %)	
	Eltrombopag	**Placebo**	**Eltrombopag**	**Placebo**	**Eltrombopag**	**Placebo**
Total number of patients entering Antiviral Treatment Phase	**n = 956**	**n = 485**	**n = 450**	**n = 232**	**n = 506**	**n = 253**
	% patients achieving virologic response					
Overall SVR [d]	21	13	23	14	19	13
HCV RNA Genotype						
Genotype 2/3	35	25	35	24	34	25
Genotype 1/4/6[e]	15	8	18	10	13	7
Albumin levels [f]						
≤ 35g/L	11	8				
> 35g/L	25	16				
MELD score [f]						
≥ 10	18	10				
< 10	23	17				

a Eltrombopag given in combination with peginterferon alfa-2a (180 mcg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1200 mg daily in 2 divided doses orally)

b Eltrombopag given in combination with peginterferon alfa-2b (1.5 mcg/kg once weekly for 48 weeks for genotype 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1400 mg orally in 2 divided doses)

c Target platelet count was ≥ 90,000/µl for ENABLE 1 and ≥ 100,000/µl for ENABLE 2. For ENABLE 1, 682 patients were randomised to the antiviral treatment phase; however 2 subjects then withdrew consent prior to receiving antiviral therapy.

d *P* value < 0.05 for eltrombopag versus placebo

e 64 % subjects participating in ENABLE 1 and ENABLE 2 were genotype 1

f Post-hoc analyses

Other secondary findings of the studies included the following; significantly fewer patients treated with eltrombopag prematurely discontinued antiviral therapy compared to placebo (45 % vs. 60 %, p = < 0.0001). A greater proportion of patients on eltrombopag did not require any antiviral dose reduction as compared to placebo (45 % versus 27 %). Eltrombopag treatment delayed and reduced the number of peginterferon dose reductions.

Severe Aplastic Anaemia

Eltrombopag was studied in a single-arm, single-centre open-label trial in 43 patients with severe aplastic anaemia with refractory thrombocytopenia following at least one prior immunosuppressive therapy (IST) and who had a platelet count ≤ 30,000/µl.

The majority of subjects, 33 (77%), were considered to have 'primary refractory disease', defined as having no prior adequate response to IST in any lineage. The remaining 10 subjects had insufficient platelet response to prior therapies. All 10 had received at least 2 prior IST regimens and 50% had received at least 3 prior IST regimens. Patients with diagnosis of Fanconi anemia, infection not responding to appropriate therapy, PNH clone size in neutrophils of ≥50%, where excluded from participation.

At baseline the median platelet count was 20,000/µl, haemoglobin was 8.4 g/dL, ANC was 0.58 x 10^9/L and absolute reticulocyte count was 24.3 x10^9/L. Eighty-six percent of patients were RBC transfusion dependent, and 91 % were platelet transfusion dependent. The majority of patients (84 %) had received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline.

The primary endpoint was haematological response assessed after 12 weeks of eltrombopag treatment. Haematological response was defined as meeting one or more of the following criteria: 1) platelet count increases to 20,000/µl above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) haemoglobin increase by > 1.5g/dL, or a reduction in ≥ 4 units of red blood cell (RBC) transfusions for 8 consecutive weeks; 3) absolute neutrophil count (ANC) increase of 100 % or an ANC increase > 0.5 x 10^9/L.

The haematological response rate was 40 % (17/43 patients; 95 % CI 25, 56), the majority were unilineage responses (13/17, 76%) whilst there were 3 bilineage and 1 trilineage responses at week 12. Eltrombopag was discontinued after 16 weeks if no haematological response or transfusion independence was observed. Patients who responded continued therapy in an extension phase of the study. A total of 14 patients entered the extension phase of the trial. Nine of these patients achieved a multi-lineage response, 4 of the 9 remain on treatment and 5 tapered off treatment with eltrombopag and maintained the response (median follow up: 20.6 months, range: 5.7 to 22.5 months). The remaining 5 patients discontinued treatment, three due to relapse at the month 3 extension visit.

During treatment with eltrombopag 59 % (23/39) became platelet transfusion independent (28 days without platelet transfusion) and 27 % (10/37) became RBC transfusion independent (56 days without RBC transfusion). The longest platelet transfusion free period for non-responders was 27 days (median). The longest platelet transfusion free period for responders was 287 days (median). The longest RBC transfusion free period for non-responders was 29 days (median). The longest RBC transfusion free period for responders was 266 days (median).

Over 50% of responders who were transfusion dependent at baseline, had >80% reduction in both platelet and RBC transfusion requirements compared to baseline.

Preliminary results from a supportive study (Study ELT116826), an ongoing non-randomised, phase II, single-arm, open-label study in refractory SAA subjects, showed consistent results. Data are limited to 21 out of the planned 60 patients with haematological responses reported by 52% of patients at 6 months. Multilineage responses were reported by 45% of patients.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Revolade in one or more subsets of the paediatric population in chronic idiopathic thrombocytopenic purpura (ITP) and Secondary Thrombocytopenia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Pharmacokinetics

The plasma eltrombopag concentration-time data collected in 88 patients with ITP in Studies TRA100773A and TRA100773B were combined with data from 111 healthy adult subjects in a population PK analysis. Plasma eltrombopag $AUC_{(0-\tau)}$ and C_{max} estimates for ITP patients are presented (Table 7).

Table 7: Geometric mean (95 % confidence intervals) of steady-state plasma eltrombopag pharmacokinetic parameters in adults with ITP

Eltrombopag dose, once daily	N	$AUC_{(0-\tau)}$[a], µg.h/ml	C_{max}[a], µg/ml
30 mg	28	47 (39, 58)	3.78 (3.18, 4.49)
50 mg	34	108 (88, 134)	8.01 (6.73, 9.53)
75 mg	26	168 (143, 198)	12.7 (11.0, 14.5)

a - $AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates.

Plasma eltrombopag concentration-time data collected in 590 subjects with HCV enrolled in Phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from patients with HCV enrolled in the Phase II study TPL102357 and healthy adult subjects in a population PK analysis. Plasma eltrombopag C_{max} $AUC_{(0-\tau)}$ estimates for patients with HCV enrolled in the Phase 3 studies are presented for each dose studied in Table 8.

Table 8 Geometric mean (95 % CI) steady-state plasma eltrombopag pharmacokinetic parameters in patients with chronic HCV

Eltrombopag dose (once daily)	**N**	**$AUC_{(0-\tau)}$ (µg.h/ml)**	**C_{max} (µg/ml)**
25 mg	330	118 (109, 128)	6.40 (5.97, 6.86)
50 mg	119	166 (143, 192)	9.08 (7.96, 10.35)
75 mg	45	301 (250, 363)	16.71 (14.26, 19.58)
100 mg	96	354 (304, 411)	19.19 (16.81, 21.91)

Data presented as geometric mean (95 % CI).
$AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates at the highest dose in the data for each patient.

Absorption and bioavailability

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure (see section 4.2). The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52 %.

Distribution

Eltrombopag is highly bound to human plasma proteins (> 99.9 %), predominantly to albumin. Eltrombopag is a substrate for BCRP, but is not a substrate for P-glycoprotein or OATP1B1.

Biotransformation

Eltrombopag is primarily metabolized through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64 % of plasma radiocarbon $AUC_{0-\infty}$. Minor metabolites due to glucuronidation and oxidation were also detected. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for oxidative metabolism of eltrombopag. Uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 are responsible for glucuronidation, and bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathway.

Elimination

Absorbed eltrombopag is extensively metabolised. The predominant route of eltrombopag excretion is via faeces (59 %) with 31 % of the dose found in the urine as metabolites. Unchanged parent compound (eltrombopag) is not detected in urine. Unchanged eltrombopag excreted in faeces accounts for approximately 20 % of the dose. The plasma elimination half-life of eltrombopag is approximately 21-32 hours.

Pharmacokinetic interactions

Based on a human study with radiolabelled eltrombopag, glucuronidation plays a minor role in the metabolism of eltrombopag. Human liver microsome studies identified UGT1A1 and UGT1A3 as the enzymes responsible for eltrombopag glucuronidation. Eltrombopag was an inhibitor of a number of UGT enzymes *in vitro*. Clinically significant drug interactions involving glucuronidation are not anticipated due to limited contribution of individual UGT enzymes in the glucuronidation of eltrombopag.

Approximately 21 % of an eltrombopag dose could undergo oxidative metabolism. Human liver microsome studies identified CYP1A2 and CYP2C8 as the enzymes responsible for eltrombopag oxidation. Eltrombopag does not inhibit or induce CYP enzymes based on *in vitro* and *in vivo* data (see section 4.5).

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter and an inhibitor of the BCRP transporter and eltrombopag increased exposure of the OATP1B1 and BCRP substrate rosuvastatin in a clinical drug interaction study (see section 4.5). In clinical studies with eltrombopag, a dose reduction of statins by 50 % was recommended.

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc (see sections 4.2 and 4.5).

Administration of a single 50 mg dose of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag $AUC_{(0-\infty)}$ and C_{max}. Whereas, low-calcium food [< 50 mg calcium] did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see sections 4.2 and 4.5).

Special patient populations

Renal impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with renal impairment. Following administration of a single 50 mg-dose, the $AUC_{0-\infty}$ of eltrombopag was 32 % to 36 % lower in subjects with mild to moderate renal impairment, and 60 % lower in subjects with severe renal impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with renal impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or urine analysis (see section 4.2). The efficacy and safety of eltrombopag has not been established in subjects with both moderate to severe renal impairment and hepatic impairment.

Hepatic impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with hepatic impairment. Following the administration of a single 50 mg dose, the $AUC_{0-\infty}$ of eltrombopag was 41 % higher in subjects with mild hepatic impairment and 80 % to 93 % higher in subjects with moderate to severe hepatic impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with hepatic impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured.

The influence of hepatic impairment on the pharmacokinetics of eltrombopag following repeat administration was evaluated using a population pharmacokinetic analysis in 28 healthy adults and 714 patients with hepatic impairment (673 patients with HCV and 41 patients with chronic liver disease of other aetiology). Of the 714 patients, 642 were with mild hepatic impairment, 67 with moderate hepatic impairment, and 2 with severe hepatic impairment. Compared to healthy volunteers, patients with mild hepatic impairment had approximately 111 % (95 % CI: 45 % to 283 %) higher plasma eltrombopag $AUC_{(0-\tau)}$ values and patients with moderate hepatic impairment had approximately 183 % (95 % CI: 90 % to 459 %) higher plasma eltrombopag $AUC_{(0-\tau)}$ values.

Therefore, eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see sections 4.2 and 4.4). For patients with HCV initiate eltrombopag at a dose of 25 mg once daily (see section 4.2).

Race

The influence of East Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (31 East Asians) and 88 patients with ITP (18 East Asians). Based on estimates from the population pharmacokinetic analysis, East Asian (i.e. Japanese, Chinese, Taiwanese and Korean) ITP patients had approximately 87 % higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East Asian patients who were predominantly Caucasian, without adjustment for body weight differences (see section 4.2).

The influence of East Asian ethnicity (such as Chinese, Japanese, Taiwanese, Korean, and Thai) on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 635 patients with HCV (145 East Asians and 69 Southeast Asians). Based on estimates from the population pharmacokinetic analysis, East Asian patients had approximately 55 % higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to patients of other races who were predominantly Caucasian (see section 4.2).

Gender

The influence of gender on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (14 females) and 88 patients with ITP (57 females). Based on estimates from the population pharmacokinetic analysis, female ITP patients had approximately 50 % higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients, without adjustment for body weight differences.

The influence of gender on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 635 patients with HCV (260 females). Based on model estimate, female HCV patient had approximately 41 % higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients.

Age

The influence of age on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 28 healthy subjects, 673 patients with HCV, and 41 patients with chronic liver disease of other aetiology ranging from 19 to 74 years old. There are no PK data on the use of eltrombopag in patients ≥ 75 years. Based on model estimate, elderly (≥ 65 years) patients had approximately 41 % higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to younger patients (see section 4.2).

5.3 Preclinical safety data

Eltrombopag does not stimulate platelet production in mice, rats or dogs because of unique TPO receptor specificity. Therefore, data from these animals do not fully model potential adverse effects related to the pharmacology of eltrombopag in humans, including the reproduction and carcinogenicity studies.

Treatment-related cataracts were detected in rodents and were dose and time-dependent. At ≥ 6 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 6 weeks and rats after 28 weeks of dosing. At ≥ 4 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human exposure in HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing. Cataracts have not been observed in dogs after 52 weeks of dosing at 2 times the human clinical exposure in ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC).

Renal tubular toxicity was observed in studies of up to 14 days duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2 year oral carcinogenicity study in mice at doses of 25, 75 and 150 mg/kg/day. Effects were less severe at lower doses and were characterized by a spectrum of regenerative changes. The exposure at the lowest dose was 1.2 times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 0.6 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC. Renal effects were not observed in rats after 28 weeks or in dogs after 52 weeks at exposures 4 and 2 times the human clinical exposure in ITP patients at 75 mg/day and 2 times and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Hepatocyte degeneration and/or necrosis, often accompanied by increased serum liver enzymes, was observed in mice, rats and dogs at doses that were associated with morbidity and mortality or were poorly tolerated. No hepatic effects were observed after chronic dosing in rats (28 weeks) and in dogs (52 weeks) at 4 or 2 times the human clinical exposure in ITP patients at 75 mg/day and 2 times and equivalent to, the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

At poorly tolerated doses in rats and dogs (> 10 times the human clinical exposure in ITP patients at 75 mg/day and> 4 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC), decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (rats only) were observed in short term studies. There were no effects of note on red cell mass or reticulocyte counts after dosing for up to 28 weeks in rats, 52 weeks in dogs and 2 years in mice or rats at maximally tolerated doses which were 2 to 4 times human clinical exposure in ITP patients at 75 mg/day and ≤ 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Endosteal hyperostosis was observed in a 28 week toxicity study in rats at a non-tolerated dose of 60 mg/kg/day (6 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). There were no bone changes observed in mice or rats after lifetime exposure (2 years) at 4 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two in vivo assays in rats (micronucleus and unscheduled DNA synthesis, 10 times the human clinical exposure in ITP patients at 75 mg/day and 7 times the human clinical exposure in HCV patients at 100 mg/day, based on C_{max}). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally positive (< 3-fold increase in mutation frequency). These *in vitro* and *in vivo* findings suggest that eltrombopag does not pose a genotoxic risk to humans.

Eltrombopag did not affect female fertility, early embryonic development or embryofoetal development in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure in ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Also there was no effect on embryofoetal development in rabbits at doses up to 150 mg/kg/day, the highest dose tested (0.3 to 0.5 times the human clinical exposure in ITP patients at 75 mg/day and HCV Patients at 100 mg/day, based on AUC). However, at a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) in rats, eltrombopag treatment was associated with embryo lethality (increased pre- and post-implantation loss), reduced foetal body weight and gravid uterine weight in the female fertility study and a low incidence of cervical ribs and reduced foetal body weight in the embryofoetal development study. Eltrombopag should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus (see section 4.6). Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). In the pre- and post-natal development study in rats, there were no undesirable effects on pregnancy, parturition or lactation of F_0 female rats at maternally non-toxic doses (10 and 20 mg/kg/day) and no effects on the growth, development, neurobehavioral or reproductive function of the offspring (F_1). Eltrombopag was detected in the plasma of all F_1 rat pups for the entire 22 hour sampling period following administration of medicinal product to the F_0 dams, suggesting that rat pup exposure to eltrombopag was likely via lactation.

In vitro studies with eltrombopag suggest a potential phototoxicity risk; however, in rodents there was no evidence of cutaneous phototoxicity (10 times the human clinical exposure in ITP patients at 75 mg/day and 5 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) or ocular phototoxicity (≥ 5 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Furthermore, a clinical pharmacology study in 36 subjects showed no evidence that photosensitivity was increased following administration of eltrombopag 75 mg. This was measured by delayed phototoxic index. Nevertheless, a potential risk of photoallergy cannot be ruled out since no specific preclinical study could be performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Magnesium stearate
Mannitol (E421)
Microcrystalline cellulose
Povidone (K30)
Sodium starch glycolate Type A

Tablet coating
Hypromellose
Iron oxide red (E172)
Iron oxide yellow (E172)
Macrogol 400
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminum blisters (PA/Alu/PVC/Alu) in a carton containing 14 or 28 film-coated tablets and multipacks containing 84 (3 packs of 28) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/004
EU/1/10/612/005
EU/1/10/612/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 March 2010
Date of latest renewal: 15 January 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

Revolade 75 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Round, biconvex, pink film-coated tablet debossed with 'GS FFS' and '75' on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Revolade is indicated for adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) splenectomised patients who are refractory to other treatments (e.g. corticosteroids, immunoglobulins). Revolade may be considered as second line treatment for adult non-splenectomised patients where surgery is contraindicated.

Revolade is indicated in adult patients with chronic hepatitis C virus (HCV) infection for the treatment of thrombocytopenia, where the degree of thrombocytopenia is the main factor preventing the initiation or limiting the ability to maintain optimal interferon-based therapy (see sections 4.4 and 5.1).

Revolade is indicated in adult patients with acquired severe aplastic anaemia (SAA) who were either refractory to prior immunosuppressive therapy or heavily pretreated and are unsuitable for haematopoietic stem cell transplantation (see section 5.1).

4.2 Posology and method of administration

Eltrombopag treatment should be initiated and remain under the supervision of a physician who is experienced in the treatment of haematological diseases or the management of chronic hepatitis C and its complications.

Posology

Eltrombopag dosing requirements must be individualised based on the patient's platelet counts. The objective of treatment with eltrombopag should not be to normalise platelet counts.

In most patients, measurable elevations in platelet counts take 1-2 weeks (see section 5.1).

Chronic immune (idiopathic) thrombocytopenia

The lowest dose of eltrombopag to achieve and maintain a platelet count ≥ 50,000/µl should be used. Dose adjustments are based upon the platelet count response. Do not use eltrombopag to normalise platelet counts. In clinical studies, platelet counts generally increased within 1 to 2 weeks after starting eltrombopag and decreased within 1 to 2 weeks after discontinuation.

The recommended starting dose of eltrombopag is 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2).

Monitoring and dose adjustment

After initiating eltrombopag, adjust the dose to achieve and maintain a platelet count ≥ 50,000/µl as necessary to reduce the risk for bleeding. Do not exceed a dose of 75 mg daily.

Clinical haematology and liver tests should be monitored regularly throughout therapy with eltrombopag and the dose regimen of eltrombopag modified based on platelet counts as outlined in Table 1. During therapy with eltrombopag full blood counts (FBCs), including platelet count and peripheral blood smears, should be assessed weekly until a stable platelet count (≥50,000/µl for at least 4 weeks) has been achieved. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter.

The lowest effective dosing regimen to maintain platelet counts should be used as clinically indicated.

Table 1 Dose adjustments of eltrombopag in ITP patients

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 75 mg/day.
≥ 50,000/µl to ≤ 150,000/µl	Use lowest dose of eltrombopag and/or concomitant ITP treatment to maintain platelet counts that avoid or reduce bleeding.
> 150,000/µl to ≤ 250,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 250,000/µl	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 25 mg.

Eltrombopag can be administered in addition to other ITP medicinal products. The dose regimen of concomitant ITP medicinal products should be modified, as medically appropriate, to avoid excessive increases in platelet counts during therapy with eltrombopag.

Wait for at least 2 weeks to see the effect of any dose adjustment on the patient's platelet response prior to considering another dose adjustment.

The standard eltrombopag dose adjustment, either decrease or increase, would be 25 mg once daily. However, in a few patients a combination of different film-coated tablet strengths on different days may be required.

Discontinuation

Treatment with eltrombopag should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of eltrombopag therapy at 75 mg once daily.

Patients should be clinically evaluated periodically and continuation of treatment should be decided on an individual basis by the treating physician. The reoccurrence of thrombocytopenia is possible upon discontinuation of treatment (see section 4.4).

Chronic hepatitis C (HCV) associated thrombocytopenia

When eltrombopag is given in combination with antivirals reference should be made to the full summary of product characteristics of the respective coadministered medicinal products for comprehensive details of relevant safety information or contraindications.

In clinical studies, platelet counts generally began to increase within 1 week of starting eltrombopag. The aim of treatment with eltrombopag should be to achieve the minimum level of platelet counts needed to initiate antiviral therapy, in adherence to clinical practice recommendations. During antiviral therapy, the aim of treatment should be to keep platelet counts at a level that prevents the risk of bleeding complications, normally around 50,000-75,000/µl. Platelet counts > 75,000/µl should be avoided. The lowest dose of eltrombopag needed to achieve the targets should be used. Dose adjustments are based upon the platelet count response.

Initial dose regimen

Eltrombopag should be initiated at a dose of 25 mg once daily. No dosage adjustment is necessary for HCV patients of East Asian ancestry or patients with mild hepatic impairment (see section 5.2).

Monitoring and dose adjustment

The dose of eltrombopag should be adjusted in 25 mg increments every 2 weeks as necessary to achieve the target platelet count required to initiate anti-viral therapy. Platelet counts should be monitored every week prior to starting antiviral therapy. On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose adjustments should be avoided (see Table 2).

During antiviral therapy, the dose of eltrombopag should be adjusted as necessary to avoid dose reductions of peginterferon due to decreasing platelet counts that may put patients at risk of bleeding (see Table 2). Platelet counts should be monitored weekly during antiviral therapy until a stable platelet count is achieved, normally around 50,000-75,000/µl. FBCs including platelet counts and peripheral blood smears should be obtained monthly thereafter. Dose reductions on the daily dose by 25 mg should be considered if platelet counts exceed the required target. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.

Do not exceed a dose of 100 mg eltrombopag once daily.

Table 2 Dose adjustments of eltrombopag in HCV patients during antiviral therapy

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 25 mg to a maximum of 100 mg/day.
≥ 50,000/µl to ≤ 100,000/µl	Use lowest dose of eltrombopag as necessary to avoid dose reductions of peginterferon
> 100,000/µl to ≤ 150,000/µl	Decrease the daily dose by 25 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments♦.
> 150,000/µl	Stop eltrombopag; increase the frequency of platelet monitoring to twice weekly. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 25 mg*.

* - For patients taking 25 mg eltrombopag once daily, consideration should be given to reinitiating dosing at 25 mg every other day.

♦ - On initiation of antiviral therapy the platelet count may fall, so immediate eltrombopag dose reductions should be avoided.

Discontinuation

If after 2 weeks of eltrombopag therapy at 100 mg the required platelet level to initiate antiviral therapy is not achieved, eltrombopag should be discontinued.

Eltrombopag treatment should be terminated when antiviral therapy is discontinued unless otherwise justified. Excessive platelet count responses or important liver test abnormalities also necessitate discontinuation.

Severe Aplastic Anaemia

Initial Dose Regimen

Initiate eltrombopag at a dose of 50 mg once daily. For patients of East Asian ancestry, eltrombopag should be initiated at a reduced dose of 25 mg once daily (see section 5.2). The treatment should not be initiated when the patients have existing cytogenetic abnormalities of chromosome 7.

Monitoring and dose adjustment

Haematological response requires dose titration, generally up to 150 mg, and may take up to 16 weeks after starting eltrombopag (see section 5.1). Adjust the dose of eltrombopag in 50 mg increments every 2 weeks as necessary to achieve the target platelet count ≥ 50,000/µl. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg. Do not exceed a dose of 150 mg daily. Monitor clinical haematology and liver tests regularly throughout therapy with eltrombopag and modify the dosage regimen of eltrombopag based on platelet counts as outlined in Table 3.

Table 3 Dose adjustments of eltrombopag in patients with severe aplastic anaemia

Platelet count	Dose adjustment or response
< 50,000/µl following at least 2 weeks of therapy	Increase daily dose by 50 mg to a maximum of 150 mg/day. For patients taking 25 mg once daily, increase the dose to 50 mg daily before increasing the dose amount by 50 mg.
≥ 50,000/µl to ≤ 150,000/µl	Use lowest dose of eltrombopag to maintain platelet counts.
> 150,000/µl to ≤ 250,000/µl	Decrease the daily dose by 50 mg. Wait 2 weeks to assess the effects of this and any subsequent dose adjustments.
> 250,000/µl	Stop eltrombopag; for at least one week. Once the platelet count is ≤ 100,000/µl, reinitiate therapy at a daily dose reduced by 50 mg.

Tapering for tri-lineage (white blood cells, red blood cells, and platelets) responders

For patients who achieve tri-lineage response, including transfusion independence, lasting at least 8 weeks: the dose of eltrombopag may be reduced by 50 %.

If counts remain stable after 8 weeks at the reduced dose, then discontinue eltrombopag and monitor blood counts. If platelet counts drop to < 30,000/µl, haemoglobin to < 9 g/dL or ANC < 0.5 x 10^9/L, eltrombopag may be reinitiated at the previous effective dose.

Discontinuation

If no haematological response has occurred after 16 weeks of therapy with eltrombopag, discontinue therapy. If new cytogenetic abnormalities are detected, evaluate whether continuation of eltrombopag is appropriate *(*see sections 4.4 and 4.8). Excessive platelet count responses (as outlined in Table 3) or important liver test abnormalities also necessitate discontinuation of eltrombopag (see section 4.8).

Special populations

Renal impairment

No dose adjustment is necessary in patients with renal impairment. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or performing urine analysis (see section 5.2).

Hepatic impairment

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see section 4.4).

If the use of eltrombopag is deemed necessary for ITP patients with hepatic impairment the starting dose must be 25 mg once daily. After initiating the dose of eltrombopag in patients with hepatic impairment wait 3 weeks before increasing the dose.

No dose adjustment is required for thrombocytopenic patients with chronic HCV and mild hepatic impairment (Child-Pugh score ≤ 6). Chronic HCV patients and severe aplastic anaemia patients with hepatic impairment should initiate eltrombopag at a dose of 25 mg once daily (see section 5.2). After initiating the dose of eltrombopag in patients with hepatic impairment wait 2 weeks before increasing the dose.

There is an increased risk for adverse events, including hepatic decompensation and thromboembolic events, in thrombocytopenic patients with advanced chronic liver disease treated with eltrombopag, either in preparation for invasive procedure or in HCV patients undergoing antiviral therapy (see sections 4.4 and 4.8).

Elderly

There are limited data on the use of eltrombopag in ITP patients aged 65 years and older and no clinical experience in ITP patients aged over 85 years. In the clinical studies of eltrombopag, overall no clinically significant differences in safety of eltrombopag were observed between subjects aged at least 65 years and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see section 5.2).

There are limited data on the use of eltrombopag in HCV and SAA patients aged over 75 years. Caution should be exercised in these patients (see section 4.4).

East Asian patients

For patients of East Asian ancestry (such as Chinese, Japanese, Taiwanese, Korean or Thai), including those with hepatic impairment, eltrombopag should be initiated at a dose of 25 mg once daily (see section 5.2).

Patient platelet count should continue to be monitored and the standard criteria for further dose modification followed.

Paediatric population

The safety and efficacy of eltrombopag has not been established in children and adolescents (< 18 years). No data are available.

Method of administration

Oral use. Eltrombopag should be taken at least four hours before or after any products such as antacids, dairy products (or other calcium containing food products), or mineral supplements containing polyvalent cations (e.g. iron, calcium, magnesium, aluminium, selenium and zinc) (see sections 4.5 and 5.2).

4.3 Contraindications

Hypersensitivity to eltrombopag or to any of the excipients, listed in section 6.1.

4.4 Special warnings and precautions for use

There is an increased risk for adverse reactions, including potentially fatal hepatic decompensation and thromboembolic events, in thrombocytopenic HCV patients with advanced chronic liver disease, as defined by low albumin levels ≤ 35 g/L or MELD score ≥ 10, when treated with eltrombopag in combination with interferon-based therapy. In addition, the benefits of treatment in terms of the proportion achieving sustained virological response (SVR) compared with placebo were modest in these patients (especially for those with baseline albumin ≤ 35g/L) compared with the group overall. Treatment with eltrombopag in these patients should be initiated only by physicians experienced in the management of advanced HCV, and only when the risks of thrombocytopenia or withholding antiviral therapy necessitate intervention. If treatment is considered clinically indicated, close monitoring of these patients is required.

Combination with direct acting antiviral agents

Safety and efficacy have not been established in combination with direct acting antiviral agents approved for treatment of chronic hepatitis C infection.

Risk of hepatotoxicity

Eltrombopag administration can cause abnormal liver function. In the controlled clinical studies in chronic ITP with eltrombopag, increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin were observed (see section 4.8).

These findings were mostly mild (Grade 1-2), reversible and not accompanied by clinically significant symptoms that would indicate an impaired liver function. Across the 3 placebo-controlled studies in chronic ITP, 1 patient in the placebo group and 1 patient in the eltrombopag group experienced a Grade 4 liver test abnormality.

In 2 controlled clinical studies in patients with HCV, ALT or AST ≥ 3 x ULN was reported in 34 % and 38 % of the eltrombopag and placebo groups, respectively. Most patients receiving eltrombopag in combination with peginterferon / ribavirin therapy will experience indirect hyperbilirubinaemia. Overall, total bilirubin ≥ 1.5 x ULN was reported in 76 % and 50 % of the eltrombopag and placebo groups, respectively.

Serum ALT, AST and bilirubin should be measured prior to initiation of eltrombopag, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose. Eltrombopag inhibits UGT1A1 and OATP1B1, which may lead to indirect hyperbilirubinaemia. If bilirubin is elevated perform fractionation. Abnormal serum liver tests should be evaluated with repeat testing within 3 to 5 days. If the abnormalities are confirmed, serum liver tests should be monitored until the abnormalities resolve, stabilise, or return to baseline levels. Eltrombopag should be discontinued if ALT levels increase (≥ 3X ULN in patients with normal liver function or ≥ 3X baseline in patients with pre-treatment elevations in transaminases) and are:

- progressive, or
- persistent for ≥ 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation

Exercise caution when administering eltrombopag to patients with hepatic disease. In ITP and SAA patients use a lower starting dose of eltrombopag and monitor closely when administering to patients with hepatic impairment (see section 4.2).

Hepatic decompensation (use with interferon)

Hepatic decompensation in patients with chronic hepatitis C: Monitor patients with low albumin levels (≤ 35 g/L) or with Model for End Stage Liver Disease (MELD) score ≥ 10 at baseline.

Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently in the eltrombopag arm (11 %) than in the placebo arm (6 %). In patients with low albumin levels (≤ 35 g/L) or MELD score ≥ 10 at baseline, there was a three-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. In addition, the benefits of treatment in terms of the proportion achieving SVR compared with placebo were modest in these patients (especially for those with baseline albumin ≤ 35g/L) compared with the group overall. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation. The respective interferon summary of product characteristics should be referenced for discontinuation criteria. Eltrombopag should be terminated if antiviral therapy is discontinued for hepatic decompensation.

Thrombotic/Thromboembolic complications

In controlled studies in thrombocytopenic patients with HCV receiving interferon-based therapy (n = 1439), 38 out of 955 subjects (4 %) treated with eltrombopag and 6 out of 484 subjects (1 %) in the placebo group experienced thromboembolic events (TEEs). Reported thrombotic/thromboembolic complications included both venous and arterial events. The majority of TEEs were non-serious and resolved by the end of the study. Portal vein thrombosis was the most common TEE in both treatment groups (2 % in patients treated with eltrombopag versus < 1 % for placebo). No specific temporal relationship between start of treatment and event of TEE were observed. Patients with low albumin levels (≤ 35 g/L) or MELD ≥ 10 had a twofold greater risk of TEEs than those with higher albumin levels; those aged ≥ 60 years had a 2-fold greater risk of TEEs compared to younger patients. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients should be closely monitored for signs and symptoms of TEE.

The risk of TEEs has been found to be increased in patients with chronic liver disease (CLD) treated with 75 mg eltrombopag once daily for two weeks in preparation for invasive procedures. Six of 143 (4 %) adult patients with CLD receiving eltrombopag experienced TEEs (all of the portal venous system) and two of 145 (1 %) subjects in the placebo group experienced TEEs (one in the portal venous system and one myocardial infarction). Five of the 6 patients treated with eltrombopag experienced the thrombotic complication at a platelet count > 200,000/µl and within 30 days of the last dose of eltrombopag. Eltrombopag is not indicated for the treatment of thrombocytopenia in patients with chronic liver disease in preparation for invasive procedures.

In eltrombopag clinical trials in ITP thromboembolic events were observed at low and normal platelet counts. Caution should be used when administering eltrombopag to patients with known risk factors for thromboembolism including but not limited to inherited (e.g. Factor V Leiden) or acquired risk factors (e.g. ATIII deficiency, antiphospholipid syndrome), advanced age, patients with prolonged periods of immobilisation, malignancies, contraceptives and hormone replacement therapy, surgery/trauma, obesity and smoking. Platelet counts should be closely monitored and consideration given to reducing the dose or discontinuing eltrombopag treatment if the platelet count exceeds the target levels (see section 4.2). The risk-benefit balance should be considered in patients at risk of thromboembolic events (TEEs) of any aetiology.

Eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. When treatment is considered appropriate, exercise caution when administering eltrombopag to patients with hepatic impairment (see sections 4.2 and 4.8).

Bleeding following discontinuation of eltrombopag

Thrombocytopenia is likely to reoccur in ITP patients upon discontinuation of treatment with eltrombopag. Following discontinuation of eltrombopag, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increase the bleeding risk and in some cases may lead to bleeding. This risk is increased if eltrombopag treatment is discontinued in the presence of anticoagulants or anti-platelet agents. It is recommended that, if treatment with eltrombopag is discontinued, ITP treatment be restarted according to current treatment guidelines. Additional medical management may include cessation of anticoagulant and/or anti-platelet therapy, reversal of anticoagulation, or platelet support. Platelet counts must be monitored weekly for 4 weeks following discontinuation of eltrombopag.

In HCV clinical trials, a higher incidence of gastrointestinal bleeding, including serious and fatal cases, was reported following discontinuation of peginterferon, ribavirin, and eltrombopag. Following discontinuation of therapy, patients should be monitored for any signs or symptoms of gastrointestinal bleeding.

Bone marrow reticulin formation and risk of bone marrow fibrosis

Eltrombopag may increase the risk for development or progression of reticulin fibres within the bone marrow. The relevance of this finding, as with other thrombopoietin receptor (TPO-R) agonists, has not been established yet.

Prior to initiation of eltrombopag, the peripheral blood smear should be examined closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable dose of eltrombopag, full blood count (FBC) with white blood cell count (WBC) differential should be performed monthly. If immature or dysplastic cells are observed, peripheral blood smears should be examined for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s). If the patient develops new or worsening morphological abnormalities or cytopenia(s), treatment with eltrombopag should be discontinued and a bone marrow biopsy considered, including staining for fibrosis.

Progression of existing Myelodysplastic Syndrome (MDS)

TPO-R agonists are growth factors that lead to thrombopoietic progenitor cell expansion, differentiation and platelet production. The TPO-R is predominantly expressed on the surface of cells of the myeloid lineage. For TPO-R agonists there is a concern that they may stimulate the progression of existing haematopoietic malignancies such as MDS.

In clinical studies with a TPO-R agonist in patients with MDS, cases of transient increases in blast cell counts were observed and cases of MDS disease progression to acute myeloid leukaemia (AML) were reported.

The diagnosis of ITP or SAA in adults and elderly patients should be confirmed by the exclusion of other clinical entities presenting with thrombocytopenia, in particular the diagnosis of MDS must be excluded. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms, or abnormal signs such as increased peripheral blast cells.

The effectiveness and safety of eltrombopag have not been established for use in other thrombocytopenic conditions including chemotherapy-induced thrombocytopenia or MDS. Eltrombopag should not be used outside of clinical trials for the treatment of thrombocytopenia due to MDS or any other cause of thrombocytopenia other than the approved indications.

Cytogenetic abnormalities and progression to MDS/AML in patients with SAA:

Cytogenetic abnormalities are known to occur in SAA patients. It is not known whether eltrombopag increases the risk of cytogenetic abnormalities in patients with SAA. In the phase II SAA clinical study with eltrombopag, the incidence of new cytogenetic abnormalities was observed in 19% of patients [8/43 (where 5 of them had changes in chromosome 7)]. The median time on study to a cytogenetic abnormality was 2.9 months.

In clinical trials with eltrombopag in SAA, 4% of patients (5/133) were diagnosed with MDS. The median time to diagnosis was 3 months from the start of eltrombopag treatment.

For SAA patients refractory to or heavily pretreated with prior immunosuppressive therapy, bone marrow examination with aspirations for cytogenetics is recommended prior to initiation of eltrombopag, at 3 months of treatment and 6 months thereafter. If new cytogenetic abnormalities are detected, evaluate whether continuation of eltrombopag is appropriate.

Ocular changes

Cataracts were observed in toxicology studies of eltrombopag in rodents (see section 5.3). In controlled studies in thrombocytopenic patients with HCV receiving interferon therapy (n = 1439), progression of pre-existing baseline cataract(s) or incident cataracts was reported in 8 % of the eltrombopag group and 5 % of the placebo group. Retinal haemorrhages, mostly Grade 1 or 2, have been reported in HCV patients receiving interferon, ribavirin and eltrombopag (2 % of the eltrombopag group and 2 % of the placebo group. Haemorrhages occurred on the surface of the retina (preretinal), under the retina (subretinal), or within the retinal tissue. Routine ophthalmologic monitoring of patients is recommended.

QT/QTc prolongation

A QTc study in healthy volunteers dosed 150 mg eltrombopag per day did not show a clinically significant effect on cardiac repolarisation. QTc interval prolongation has been reported in clinical trials of patients with ITP and thrombocytopenic patients with HCV. The clinical significance of these QTc prolongation events is unknown.

Loss of response to eltrombopag

A loss of response or failure to maintain a platelet response with eltrombopag treatment within the recommended dosing range should prompt a search for causative factors, including an increased bone marrow reticulin.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of eltrombopag on other medicinal products

HMG CoA reductase inhibitors

In vitro studies demonstrated that eltrombopag is not a substrate for the organic anion transporter polypeptide, OATP1B1, but is an inhibitor of this transporter. *In vitro* studies also demonstrated that eltrombopag is a breast cancer resistance protein (BCRP) substrate and inhibitor. Administration of eltrombopag 75 mg once daily for 5 days with a single 10 mg dose of the OATP1B1 and BCRP substrate rosuvastatin to 39 healthy adult subjects increased plasma rosuvastatin C_{max} 103 % (90 % confidence interval [CI]: 82 %, 126 %) and $AUC_{0-\infty}$ 55 % (90 % CI: 42 %, 69 %). Interactions are also expected with other HMG-CoA reductase inhibitors, including atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin. When co-administered with eltrombopag, a reduced dose of statins should be considered and careful monitoring for statin adverse reactions should be undertaken (see section 5.2).

OATP1B1 and BCRP substrates

Concomitant administration of eltrombopag and OATP1B1 (e.g. methotrexate) and BCRP (e.g. topotecan and methotrexate) substrates should be undertaken with caution (see section 5.2).

Cytochrome P450 substrates

In studies utilizing human liver microsomes, eltrombopag (up to 100 μM) showed no *in vitro* inhibition of the CYP450 enzymes 1A2, 2A6, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11 and was an inhibitor of CYP2C8 and CYP2C9 as measured using paclitaxel and diclofenac as the probe substrates. Administration of eltrombopag 75 mg once daily for 7 days to 24 healthy male subjects did not inhibit or induce the metabolism of probe substrates for 1A2 (caffeine), 2C19 (omeprazole), 2C9 (flurbiprofen), or 3A4 (midazolam) in humans. No clinically significant interactions are expected when eltrombopag and CYP450 substrates are co-administered (see section 5.2).

HCV Protease Inhibitors

Dose adjustment is not required when eltrombopag is co-administered with either telaprevir or boceprevir. Co-administration of a single dose of eltrombopag 200 mg with telaprevir 750 mg Q8h did not alter plasma telaprevir exposure.

Co-administration of a single dose of eltrombopag 200 mg with boceprevir 800 mg Q8h did not alter plasma boceprevir $AUC_{(0-\tau)}$, but increased C_{max} by 20 %, and decreased C_{min} by 32 %. The clinical relevance of the decrease in C_{min} has not been established, increased clinical and laboratory monitoring for HCV suppression is recommended.

Effects of other medicinal products on eltrombopag

Polyvalent cations (chelation)

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc. Administration of a single dose of eltrombopag 75 mg with a polyvalent cation-containing antacid (1524 mg aluminium hydroxide and 1425 mg magnesium carbonate) decreased plasma eltrombopag $AUC_{0-\infty}$ by 70 % (90 % CI: 64 %, 76 %) and C_{max} by 70 % (90 % CI: 62 %, 76 %). Antacids, dairy products and other products containing polyvalent cations, such as mineral supplements, must be administered at least four hours apart from eltrombopag dosing to avoid significant reduction in eltrombopag absorption due to chelation (see sections 4.2 and 5.2).

Food interaction

Administration of a single 50 mg-dose of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag $AUC_{0-\infty}$ by 59 % (90 % CI: 54 %, 64 %) and C_{max} by 65 % (90 % CI: 59 %, 70 %). Food low in calcium [< 50 mg calcium] including fruit, lean ham, beef and unfortified (no added calcium, magnesium, iron) fruit juice, unfortified soy milk, and unfortified grain did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see sections 4.2 and 5.2).

Lopinavir/ritonavir

Co-administration of eltrombopag with lopinavir/ritonavir (LPV/RTV) may cause a decrease in the concentration of eltrombopag. A study in 40 healthy volunteers showed that the co-administration of single dose eltrombopag 100 mg with repeat dose LPV/RTV 400 /100 mg twice daily resulted in a reduction in eltrombopag plasma $AUC_{(0-\infty)}$ by 17 % (90 % CI: 6.6 %, 26.6 %). Therefore, caution should be used when co-administration of eltrombopag with LPV/RTV takes place. Platelet count should be closely monitored in order to ensure appropriate medical management of the dose of eltrombopag when lopinavir/ritonavir therapy is initiated or discontinued.

CYP1A2 and CYP2C8 inhibitors and inducers

Eltrombopag is metabolized through multiple pathways including CYP1A2, CYP2C8, UGT1A1, and UGT1A3 (see section 5.2). Medicinal products that inhibit or induce a single enzyme are unlikely to significantly affect plasma eltrombopag concentrations; whereas medicinal products that inhibit or induce multiple enzymes have the potential to increase (e.g. fluvoxamine) or decrease (e.g. rifampicin) eltrombopag concentrations.

HCV Protease Inhibitors

Results of a drug-drug pharmacokinetic (PK) interaction study show that co-administration of repeat doses of boceprevir 800 mg Q8h or telaprevir 750 mg Q8h with a single dose of eltrombopag 200 mg did not alter plasma eltrombopag exposure to a clinically significant extent.

Medicinal products for treatment of ITP

Medicinal products used in the treatment of ITP in combination with eltrombopag in clinical studies included corticosteroids, danazol, and/or azathioprine, intravenous immunoglobulin (IVIG), and anti-D immunoglobulin. Platelet counts should be monitored when combining eltrombopag with other medicinal products for the treatment of ITP in order to avoid platelet counts outside of the recommended range (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of eltrombopag in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Revolade is not recommended during pregnancy.

Women of childbearing potential / Contraception in males and females

Revolade is not recommended in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether eltrombopag/metabolites are excreted in human milk. Studies in animals have shown that eltrombopag is likely secreted into milk (see section 5.3); therefore a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to continue/abstain from Revolade therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Fertility was not affected in male or female rats at exposures that were comparable to those in humans. However a risk for humans cannot be ruled out (see section 5.3).

4.7 Effects on ability to drive and use machines

Eltrombopag has negligible influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of eltrombopag, including dizziness and lack of alertness, should be borne in mind when considering the patient's ability to perform tasks that require judgment, motor and cognitive skills.

4.8 Undesirable effects

Summary of the safety profile

Based on an analysis of all chronic ITP patients receiving eltrombopag in 4 controlled and 2 uncontrolled clinical studies, the overall incidence of adverse reactions in subjects treated with eltrombopag was 79 % (433/530). The mean duration of exposure to eltrombopag was 260 days and patient year's exposure was 390 in this study population.

ENABLE 1 (TPL103922 N=716) and ENABLE 2 (TPL108390 N=805) were randomized, double-blind, placebo-controlled, multicentre studies to assess the efficacy and safety of eltrombopag in thrombocytopenic subjects with HCV infection who were otherwise eligible to initiate antiviral therapy with interferon and ribavirin therapy.

In the HCV studies the safety population consisted of all randomized subjects who received double-blind study drug during Part 2 of ENABLE 1 (eltrombopag treatment N=449, placebo N=232) and ENABLE 2 (eltrombopag treatment N=506, placebo N=252). Subjects are analysed according to the treatment received (total safety double blind population, eltrombopag N=955 and placebo N=484).

The safety of eltrombopag in severe aplastic anaemia was assessed in a single-arm, open-label trial (N=43) in which 12 patients (28 %) were treated for > 6 months and 9 patients (21 %) were treated for > 1 year.

The most important serious adverse reactions identified in the ITP or HCV trials were hepatotoxicity and thrombotic/thromboembolic events.

The most common adverse reactions (experienced by at least 10 % of patients) of any grade in the ITP or HCV trials included; headache, anaemia, decreased appetite, insomnia, cough, nausea, diarrhoea, alopecia, pruritus, myalgia, pyrexia, fatigue, influenza like illness, asthenia, chills and peripheral oedema.

List of adverse reactions

The adverse reactions in the ITP studies (N = 550), the HCV studies (N = 955), the SAA studies (N = 43) and post-marketing reports are listed below by MedDRA system organ class and by frequency.

Very common	(≥ 1/10)
Common	(≥ 1/100 to < 1/10)
Uncommon	(≥ 1/1,000 to < 1/100)
Rare	(≥ 1/10,000 to < 1/1,000)
Very rare	(< 1/10,000)
Not known	(cannot be estimated from the available data)

ITP study population

Infections and infestations

Uncommon Pharyngitis, Urinary tract infection, Influenza, Oral herpes, Pneumonia, Sinusitis, Tonsillitis, Respiratory tract infection, Gingivitis, Skin infection

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Uncommon Rectosigmoid cancer

Blood and lymphatic system disorders

Uncommon Anaemia, Anisocytosis, Eosinophilia, Haemolytic anaemia, Leukocytosis, Myelocytosis, Thrombocytopenia, Haemoglobin increased, Band neutrophil count increased, Haemoglobin decreased, Myelocyte present, Platelet count increased, White blood cell count decreased

Immune system disorders

Uncommon Hypersensitivity

Metabolism and nutrition disorders

Uncommon Anorexia, Hypokalaemia, Decreased appetite, Gout, Hypocalcaemia, Blood uric acid increased

Psychiatric disorders

Uncommon Sleep disorder, Depression, Apathy, Mood altered, Tearfulness

Nervous systems disorders

Common Paraesthesia

Uncommon Hypoaesthesia, Somnolence, Migraine, Tremor, Balance disorder, Dysaesthesia, Hemiparesis, Migraine with aura, Neuropathy peripheral, Peripheral sensory neuropathy, Speech disorder, Toxic neuropathy, Vascular headache

Eye disorders

Common Dry eye

Uncommon Vision blurred, Lenticular opacities, Astigmatism, Cataract cortical, Eye pain, Lacrimation increased, Retinal haemorrhage, Retinal pigment epitheliopathy, Visual acuity reduced, Visual impairment, Visual acuity tests abnormal, Blepharitis and Keratoconjunctivitis sicca

Ear and labyrinth disorders

Uncommon Ear pain, Vertigo

Cardiac disorders

Uncommon Tachycardia, Acute myocardial infarction, Cardiovascular disorder, Cyanosis, Sinus tachycardia, Electrocardiogram QT prolonged

Vascular disorders

Uncommon Deep vein thrombosis, Embolism, Hot flush, Thrombophlebitis superficial, Flushing, Haematoma

Respiratory, thoracic and mediastinal disorders

Uncommon Pulmonary embolism, Pulmonary infarction, Nasal discomfort, Oropharyngeal blistering, Oropharyngeal pain, Sinus disorder, Sleep apnoea syndrome

Gastrointestinal disorders

Common Nausea, Diarrhoea, Mouth ulceration

Uncommon Dry mouth, Vomiting, Abdominal pain, Glossodynia, Mouth haemorrhage, Abdominal tenderness, Faeces discoloured, Flatulence, Food poisoning, Frequent bowel movements, Haematemesis, Oral discomfort

Hepatobiliary disorders

Common Alanine aminotransferase increased*, Aspartate aminotransferase increased*, Hyperbilirubinaemia, Hepatic function abnormal

Uncommon Cholestasis, Hepatic lesion, Hepatitis

*Increase of alanine aminotransferase and aspartate aminotransferase may occur simultaneously, although at a lower frequency.

Skin and subcutaneous tissue disorders

Common Rash, Alopecia

Uncommon Hyperhidrosis, Pruritus generalised, Urticaria, Dermatosis, Petechiae, Cold sweat, Erythema, Melanosis, Pigmentation disorder, Skin discolouration, Skin exfoliation

Musculoskeletal and connective tissue disorders

Common Myalgia, Muscle spasm, Musculoskeletal pain, Bone pain, Back pain

Uncommon Muscular weakness

Renal and urinary disorders

Uncommon Renal failure, Leukocyturia, Lupus nephritis, Nocturia, Proteinuria, Blood urea increased, Blood creatinine increased, Urine protein/creatinine ratio increased

Reproductive system and breast disorders

Common Menorrhagia

General disorders and administration site conditions

Uncommon Chest pain, Feeling hot, Vessel puncture site haemorrhage, Asthenia, Feeling jittery, Inflammation of wound, Malaise, Pyrexia, Sensation of foreign body

Investigations

Uncommon Blood albumin increased, Blood alkaline phosphatase increased, Protein total increased, Blood albumin decreased, pH urine increased

Injury, poisoning and procedural complications

Uncommon Sunburn

HCV study population (in combination with anti-viral interferon and ribavirin therapy)

Infections and infestations

Common Urinary tract infection, Upper respiratory tract infection, Bronchitis, Nasopharyngitis, Influenza, Oral herpes, Gastroenteritis, Pharyngitis

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Common Hepatic neoplasm malignant

Blood and lymphatic system disorders

Very common Anaemia
Common Lymphopenia, Haemolytic anaemia

Metabolism and nutrition disorders

Very common Decreased appetite
Common Hyperglycaemia, Abnormal loss of weight

Psychiatric disorders

Very common Insomnia
Common Depression, Anxiety, Sleep disorder, Confusional state, Agitation

Nervous systems disorders

Very common Headache
Common Dizziness, Disturbance in attention, Dysgeusia, Hepatic encephalopathy, Lethargy, Memory impairment, Paraesthesia

Eye disorders

Common Cataract, Retinal exudates, Dry Eye, Ocular icterus, Retinal haemorrhage

Ear and labyrinth disorders

Common Vertigo

Cardiac disorders

Common Palpitations

Respiratory, thoracic and mediastinal disorders

Very common Cough
Common Dyspnoea, Oropharyngeal pain, Dyspnoea exertional, Productive cough

Gastrointestinal disorders

Very common Nausea, Diarrhoea
Common Vomiting, Ascites, Abdominal pain, Abdominal pain upper, Dyspepsia, Dry mouth, Constipation, Abdominal distension, Toothache, Stomatitis, Gastrooesophagal reflux disease, Haemorrhoids, Abdominal discomfort, Gastritis, Varices oesophageal, Aphthous stomatitis, Oesophageal varices haemorrhage

Hepatobiliary disorders

Common Hyperbilirubinaemia, Jaundice, Portal vein thrombosis, Hepatic failure

Skin and subcutaneous tissue disorders

Very common Pruritus, Alopecia
Common Rash, Dry skin, Eczema, Rash pruritic, Erythema, Hyperhidrosis, Pruritus generalised, Night sweats, Skin lesion

Musculoskeletal and connective tissue disorder

Very common Myalgia
Common Arthralgia, Muscle spasms, Back pain, Pain in extremity, Musculoskeletal pain, Bone pain

Renal and urinary disorders

Uncommon Dysuria

General disorders and administration site conditions

Very common Pyrexia, Fatigue, Influenza like illness, Asthenia, Chills, Oedema peripheral
Common Irritability, Pain, Malaise, Injection site reaction, Non-cardiac chest pain, Oedema, Injection site rash, Chest discomfort, Injection site pruritus

Investigations

Common Blood bilirubin increased, Weight decreased, White blood cell count decreased, Haemoglobin decreased, Neutrophil count decreased, International normalised ratio increased, Activated partial thromboplastin time prolonged, Blood glucose increased, Blood albumin decreased, Electrocardiogram QT prolonged

SAA study population

Blood and lymphatic system disorders

Common Neutropenia, Splenic infarction

Metabolism and nutrition disorders

Common Iron overload, Decreased appetite, Hypoglycaemia, Increased appetite

Psychiatric disorders

Very common Insomnia

Common Anxiety, Depression

Nervous systems disorders

Very common Headache, Dizziness

Common Syncope

Eye disorders

Common Dry eye, Eye pruritus, Cataract, Ocular icterus, Vision blurred, Visual impairment, Vitreous floaters

Respiratory, thoracic and mediastinal disorders

Very common Cough. Dyspnoea, Oropharyngeal Pain, Rhinorrhoea

Common Epistaxis

Gastrointestinal disorders

Very common Abdominal pain, Diarrhoea, Nausea

Common Gingival bleeding, Oral mucosal blistering, Oral pain, Vomiting, Abdominal discomfort, Abdominal pain, Constipation, Abdominal distension, Dysphagia, Faeces discoloured, Swollen tongue, Gastrointestinal motility disorder, Flatulence

Hepatobiliary disorders

Very common Transaminases increased

Common Blood bilirubin increased (hyperbilirubinemia), Jaundice

Skin and subcutaneous tissue disorders

Very common	Ecchymosis
Common	Petechiae, Rash, Pruritus, Urticaria, Skin lesion, Rash Macular

Musculosketal and connective tissue disorders

Very common	Arthralgia, Muscle spasms, Pain in extremity
Common	Back pain, Myalgia, Bone pain

Renal and urinary disorders

Common	Chromaturia

General disorders and administration site conditions

Very common	Fatigue, Febrile neutropenia, Pyrexia
Common	Asthenia, Oedema peripheral, Chills, Malaise

Investigations

Common	Blood creatine phosphokinase increased

Description of selected adverse reactions

Thrombotic/Thromboembolic events (TEEs)

In 3 controlled and 2 uncontrolled clinical studies, among adult chronic ITP patients receiving eltrombopag (n = 446), 17 subjects experienced a total of 19 TEEs, which included (in descending order of occurrence) deep vein thrombosis (n = 6), pulmonary embolism (n = 6), acute myocardial infarction (n = 2), cerebral infarction (n = 2), embolism (n = 1) (see section 4.4).

In a placebo-controlled study (n = 288, Safety population), following 2 weeks treatment in preparation for invasive procedures, 6 of 143 (4 %) adult patients with chronic liver disease receiving eltrombopag experienced 7 TEEs of the portal venous system and 2 of 145 (1 %) subjects in the placebo group experienced 3 TEEs. Five of the 6 patients treated with eltrombopag experienced the TEE at a platelet count > 200,000/µl

No specific risk factors were identified in those subjects who experienced a TEE with the exception of platelet counts ≥ 200,000/µl (see section 4.4).

In controlled studies in thrombocytopenic patients with HCV (n = 1439), 38 out of 955 subjects (4 %) treated with eltrombopag experienced a TEE and 6 out of 484 subjects (1 %) in the placebo group experienced TEEs. Portal vein thrombosis was the most common TEE in both treatment groups (2 % in patients treated with eltrombopag versus < 1 % for placebo) (see section 4.4). Patients with low albumin levels (≤ 35 g/L) or MELD ≥ 10 had a twofold greater risk of TEEs than those with higher albumin levels; those aged ≥ 60 years had a 2-fold greater risk of TEEs compared to younger patients.

Hepatic decompensation (use with interferon)

Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa interferon therapy. In 2 controlled clinical studies in thrombocytopenic patients with HCV, hepatic decompensation (ascites, hepatic encephalopathy, variceal haemorrhage, spontaneous bacterial peritonitis) was reported more frequently in the eltrombopag arm (11 %) than in the placebo arm (6 %). In patients with low albumin levels (≤ 35 g/L) or Model for End-Stage Liver Disease (MELD) score ≥ 10 at baseline, there was a three-fold greater risk of hepatic decompensation and an increase in the risk of a fatal adverse event compared to those with less advanced liver disease. Eltrombopag should only be administered to such patients after careful consideration of the expected benefits in comparison with the risks. Patients with these characteristics should be closely monitored for signs and symptoms of hepatic decompensation (see section 4.4).

Thrombocytopenia following discontinuation of treatment

In the 3 controlled clinical ITP studies, transient decreases in platelet counts to levels lower than baseline were observed following discontinuation of treatment in 8 % and 8 % of the eltrombopag and placebo groups, respectively (see section 4.4).

Increased bone marrow reticulin

Across the programme, no patients had evidence of clinically relevant bone marrow abnormalities or clinical findings that would indicate bone marrow dysfunction. In one ITP patient, eltrombopag treatment was discontinued due to bone marrow reticulin (see section 4.4).

Cytogenetic abnormalities

In the single-arm, open-label trial in SAA, patients had bone marrow aspirates evaluated for cytogenetic abnormalities. Eight (19%) patients had a new cytogenetic abnormality reported, including 5 patients who had changes in chromosome 7. In the two ongoing studies (ELT116826 and ELT116643), cytogenetic abnormalities have been detected in 4/28 (14%) and 4/62 (6%) subjects in each study.

Haematologic malignancies

In the single-arm, open label trial in SAA, three (7%) patients were diagnosed with MDS following treatment with eltrombopag, in the two ongoing studies (ELT116826 and ELT116643), 1/28 (4%) and 1/62 (2%) subject has been diagnosed with MDS or AML in each study.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In case of an overdose, consider oral administration of a metal cation-containing preparation, such as calcium, aluminium, or magnesium preparations to chelate eltrombopag and thus limit absorption. Closely monitor platelet counts. Reinitiate treatment with eltrombopag in accordance with dosing and administration recommendations (see section 4.2).

In the clinical studies there was one report of overdose where the subject ingested 5000 mg of eltrombopag. Reported adverse reactions included mild rash, transient bradycardia, ALT and AST elevation, and fatigue. Liver enzymes measured between Days 2 and 18 after ingestion peaked at a 1.6-fold ULN in AST, a 3.9-fold ULN in ALT, and a 2.4-fold ULN in total bilirubin, The platelet counts were 672,000/µl on day 18 after ingestion and the maximum platelet count was 929,000/µl. All events were resolved without sequelae following treatment.

Because eltrombopag is not significantly renally excreted and is highly bound to plasma proteins, haemodialysis would not be expected to be an effective method to enhance the elimination of eltrombopag.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics, other systemic hemostatics. ATC code: B02BX 05.

Mechanism of action

TPO is the main cytokine involved in regulation of megakaryopoiesis and platelet production, and is the endogenous ligand for the TPO-R. Eltrombopag interacts with the transmembrane domain of the human TPO-R and initiates signalling cascades similar but not identical to that of endogenous thrombopoietin (TPO), inducing proliferation and differentiation from bone marrow progenitor cells.

Clinical efficacy and safety

Chronic immune (idiopathic) thrombocytopenia (ITP) studies

Two Phase III, randomised, double-blind, placebo-controlled studies RAISE (TRA102537) and TRA100773B and two open-label studies REPEAT (TRA108057) and EXTEND (TRA105325) evaluated the safety and efficacy of eltrombopag in adult patients with previously treated chronic ITP. Overall, eltrombopag was administered to 277 ITP patients for at least 6 months and 202 patients for at least 1 year.

Double-blind placebo-controlled studies

RAISE: 197 ITP patients were randomised 2:1, eltrombopag (n=135) to placebo (n=62), and randomisation was stratified based upon splenectomy status, use of ITP medicinal products at baseline and baseline platelet count. The dose of eltrombopag was adjusted during the 6 month treatment period based on individual platelet counts. All patients initiated treatment with eltrombopag 50 mg. From Day 29 to the end of treatment, 15 to 28 % of eltrombopag treated patients were maintained on ≤ 25 mg and 29 to 53 % received 75 mg.

In addition, patients could taper off concomitant ITP medicinal products and receive rescue treatments as dictated by local standard of care. More than half of all patients in each treatment group had ≥ 3 prior ITP therapies and 36 % had a prior splenectomy.

Median platelet counts at baseline were 16,000/µl for both treatment groups and in the eltrombopag group were maintained above 50,000/µl at all on-therapy visits starting at Day 15; in contrast, median platelet counts in the placebo group remained < 30,000/µl throughout the study.

Platelet count response between 50,000-400,000/μl in the absence of rescue treatment was achieved by significantly more patients in the eltrombopag treated group during the 6 month treatment period, $p < 0.001$. Fifty-four percent of the eltrombopag-treated patients and 13 % of placebo-treated patients achieved this level of response after 6 weeks of treatment. A similar platelet response was maintained throughout the study, with 52 % and 16 % of patients responding at the end of the 6-month treatment period.

Table 4: Secondary efficacy results from RAISE

	Eltrombopag N = 135	Placebo N = 62
Key secondary endpoints		
Number of cumulative weeks with platelet counts ≥ 50,000-400,000/μl, Mean (SD)	11.3 (9.46)	2.4 (5.95)
Patients with ≥ 75 % of assessments in the target range (50,000 to 400,000/μl), n (%)	51 (38)	4 (7)
P-value [a]	< 0.001	
Patients with bleeding (WHO Grades 1-4) at any time during 6 months, n (%)	106 (79)	56 (93)
P-value [a]	0.012	
Patients with bleeding (WHO Grades 2-4) at any time during 6 months, n (%)	44 (33)	32 (53)
P-value [a]	0.002	
Requiring rescue therapy, n (%)	24 (18)	25 (40)
P-value [a]	0.001	
Patients receiving ITP therapy at baseline (n)	63	31
Patients who attempted to reduce or discontinue baseline therapy, n (%)[b]	37 (59)	10 (32)
P value [a]	0.016	

a Logistic regression model adjusted for randomisation stratification variables

b 21 out of 63 (33 %) patients treated with eltrombopag who were taking an ITP medicinal product at baseline permanently discontinued all baseline ITP medicinal products.

At baseline, more than 70 % of ITP patients in each treatment group reported any bleeding (WHO Grades 1-4) and more than 20 % reported clinically significant bleeding (WHO Grades 2-4), respectively. The proportion of eltrombopag-treated patients with any bleeding (Grades 1-4) and clinically significant bleeding (Grades 2-4) was reduced from baseline by approximately 50 % from Day 15 to the end of treatment throughout the 6 month treatment period.

TRA100773B: The primary efficacy endpoint was the proportion of responders, defined as ITP patients who had an increase in platelet counts to ≥ 50,000/μl at Day 43 from a baseline of < 30,000/μl; patients who withdrew prematurely due to a platelet count > 200,000/μl were considered responders, those that discontinued for any other reason were considered non-responders irrespective of platelet count. A total of 114 patients with previously treated chronic ITP were randomised 2:1 eltrombopag (n = 76) to placebo (n = 38).

Table 5: Efficacy results from TRA100773B

	Eltrombopag N = 74	Placebo N = 38
Key primary endpoints		
Eligible for efficacy analysis, n	73	37
Patients with platelet count ≥ 50,000/µl after up to 42 days of dosing (compared to a baseline count of < 30,000/µl), n (%)	43 (59)	6 (16)
P value[a]	< 0.001	
Key secondary endpoints		
Patients with a Day 43 bleeding assessment, n	51	30
Bleeding (WHO Grades 1-4) n (%)	20 (39)	18 (60)
P value[a]	0.029	

a – Logistic regression model adjusted for randomisation stratification variables

In both RAISE and TRA100773B the response to eltrombopag relative to placebo was similar irrespective of ITP medicinal product use, splenectomy status and baseline platelet count (≤ 15,000/µl, > 15,000/µl) at randomisation.

In RAISE and TRA100773B studies, in the subgroup of ITP patients with baseline platelet count ≤ 15,000/µl the median platelet counts did not reach the target level (> 50,000/µl), although in both studies 43 % of these patients treated with eltrombopag responded after 6 weeks of treatment. In addition, in the RAISE study, 42 % of patients with baseline platelet count ≤ 15,000/µl treated with eltrombopag responded at the end of the 6 month treatment period. Forty-two to 60 % of the eltrombopag-treated patients in the RAISE study were receiving 75 mg from Day 29 to the end of treatment.

An open label, repeat dose study (3 cycles of 6 weeks of treatment, followed by 4 weeks off treatment) showed that episodic use with multiple courses of eltrombopag has demonstrated no loss of response.

Eltrombopag was administered to 299 ITP patients in an open-label extension study, 126 patients completed 1 year, 48 completed 18 months and 17 completed 2 years. The median baseline platelet count was 19,500/µl prior to eltrombopag administration. Median platelet counts at 12, 18 and 24 months on study were 68,000/µl, 75,000/µl and 119,000/µl, respectively.

Chronic hepatitis C associated thrombocytopenia studies

The efficacy and safety of eltrombopag for the treatment of thrombocytopenia in patients with HCV infection were evaluated in two randomized, double-blind, placebo-controlled studies. ENABLE 1 utilized peginterferon alfa-2a plus ribavirin for antiviral treatment and ENABLE 2 utilized peginterferon alfa-2b plus ribavirin. Patients did not receive direct acting antiviral agents. In both studies, patients with a platelet count of < 75,000/µl were enrolled and stratified by platelet count (< 50,000/µl and ≥ 50,000/µl to < 75,000/µl), screening HCV RNA (< 800,000 IU/ml and ≥ 800,000 IU/ml), and HCV genotype (genotype 2/3, and genotype 1/4/6).

Baseline disease characteristics were similar in both studies and were consistent with compensated cirrhotic HCV patient population. The majority of patients were HCV genotype 1 (64 %) and had bridging fibrosis/cirrhosis. Thirty-one percent of patients had been treated with prior HCV therapies, primarily pegylated interferon plus ribavirin. The median baseline platelet count was 59,500/µl in both treatment groups: 0.8 %, 28 % and 72 % of the patients recruited had platelet counts < 20,000/µl, < 50.000/µl and ≥ 50,000/µl respectively.

The studies consisted of two phases – a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-antiviral treatment phase, subjects received open-label eltrombopag to increase the platelet count to ≥ 90,000/µl for ENABLE 1 and ≥ 100,000/µl for ENABLE 2. The median time to achieve the target platelet count ≥ 90,000/µl (ENABLE 1) or ≥ 100,000/µl (ENABLE 2) was 2 weeks.

The primary efficacy endpoint for both studies was sustained virologic response (SVR), defined as the percentage of patients with no detectable HCV-RNA at 24 weeks after completion of the planned treatment period.

In both HCV studies, a significantly greater proportion of patients treated with eltrombopag (n = 201, 21 %) achieved SVR compared to those treated with placebo (n=65, 13 %) (see Table 6). The improvement in the proportion of patients who achieved SVR was consistent across all subgroups in the randomisation strata (baseline platelet counts (< 50,000 vs. > 50,000), viral load (< 800,000 IU/ml vs. ≥ 800,000 IU/ml) and genotype (2/3 vs. 1/4/6)).

Table 6: Virologic response in HCV patients in ENABLE 1 and ENABLE 2

	Pooled Data		**ENABLE 1[a]**		**ENABLE 2[b]**	
Patients achieving target platelet counts & initiating antiviral therapy [c]	1439/1520 (95 %)		680/715 (95 %)		759/805 (94 %)	
	Eltrombopag	**Placebo**	**Eltrombopag**	**Placebo**	**Eltrombopag**	**Placebo**
Total number of patients entering Antiviral Treatment Phase	**n = 956**	**n = 485**	**n = 450**	**n = 232**	**n = 506**	**n = 253**
	% patients achieving virologic response					
Overall SVR [d]	21	13	23	14	19	13
HCV RNA Genotype						
Genotype 2/3	35	25	35	24	34	25
Genotype 1/4/6[e]	15	8	18	10	13	7
Albumin levels [f]						
≤ 35g/L	11	8				
> 35g/L	25	16				
MELD score[f]						
≥ 10	18	10				
< 10	23	17				

a Eltrombopag given in combination with peginterferon alfa-2a (180 mcg once weekly for 48 weeks for genotypes 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1200 mg daily in 2 divided doses orally)

b Eltrombopag given in combination with peginterferon alfa-2b (1.5 mcg/kg once weekly for 48 weeks for genotype 1/4/6; 24 weeks for genotype 2/3) plus ribavirin (800 to 1400 mg orally in 2 divided doses)

c Target platelet count was ≥ 90,000/µl for ENABLE 1 and ≥ 100,000/µl for ENABLE 2. For ENABLE 1, 682 patients were randomised to the antiviral treatment phase; however 2 subjects then withdrew consent prior to receiving antiviral therapy.

d *P* value < 0.05 for eltrombopag versus placebo

e 64 % subjects participating in ENABLE 1 and ENABLE 2 were genotype 1

f Post-hoc analyses

Other secondary findings of the studies included the following; significantly fewer patients treated with eltrombopag prematurely discontinued antiviral therapy compared to placebo (45 % vs. 60 %, p = < 0.0001). A greater proportion of patients on eltrombopag did not require any antiviral dose reduction as compared to placebo (45 % versus 27 %). Eltrombopag treatment delayed and reduced the number of peginterferon dose reductions.

Severe Aplastic Anaemia

Eltrombopag was studied in a single-arm, single-centre open-label trial in 43 patients with severe aplastic anaemia with refractory thrombocytopenia following at least one prior immunosuppressive therapy (IST) and who had a platelet count ≤ 30,000/µl.

The majority of subjects, 33 (77%), were considered to have 'primary refractory disease', defined as having no prior adequate response to IST in any lineage. The remaining 10 subjects had insufficient platelet response to prior therapies. All 10 had received at least 2 prior IST regimens and 50% had received at least 3 prior IST regimens. Patients with diagnosis of Fanconi anemia, infection not responding to appropriate therapy, PNH clone size in neutrophils of ≥50%, where excluded from participation.

At baseline the median platelet count was 20,000/µl, haemoglobin was 8.4 g/dL, ANC was 0.58 x 10^9/L and absolute reticulocyte count was 24.3 x10^9/L. Eighty-six percent of patients were RBC transfusion dependent, and 91 % were platelet transfusion dependent. The majority of patients (84 %) had received at least 2 prior immunosuppressive therapies. Three patients had cytogenetic abnormalities at baseline.

The primary endpoint was haematological response assessed after 12 weeks of eltrombopag treatment. Haematological response was defined as meeting one or more of the following criteria: 1) platelet count increases to 20,000/µl above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) haemoglobin increase by > 1.5g/dL, or a reduction in ≥ 4 units of red blood cell (RBC) transfusions for 8 consecutive weeks; 3) absolute neutrophil count (ANC) increase of 100 % or an ANC increase > 0.5 x 10^9/L.

The haematological response rate was 40 % (17/43 patients; 95 % CI 25, 56), the majority were unilineage responses (13/17, 76%) whilst there were 3 bilineage and 1 trilineage responses at week 12. Eltrombopag was discontinued after 16 weeks if no haematological response or transfusion independence was observed. Patients who responded continued therapy in an extension phase of the study. A total of 14 patients entered the extension phase of the trial. Nine of these patients achieved a multi-lineage response, 4 of the 9 remain on treatment and 5 tapered off treatment with eltrombopag and maintained the response (median follow up: 20.6 months, range: 5.7 to 22.5 months). The remaining 5 patients discontinued treatment, three due to relapse at the month 3 extension visit.

During treatment with eltrombopag 59 % (23/39) became platelet transfusion independent (28 days without platelet transfusion) and 27 % (10/37) became RBC transfusion independent (56 days without RBC transfusion). The longest platelet transfusion free period for non-responders was 27 days (median). The longest platelet transfusion free period for responders was 287 days (median). The longest RBC transfusion free period for non-responders was 29 days (median). The longest RBC transfusion free period for responders was 266 days (median).

Over 50% of responders who were transfusion dependent at baseline, had >80% reduction in both platelet and RBC transfusion requirements compared to baseline.

Preliminary results from a supportive study (Study ELT116826), an ongoing non-randomised, phase II, single-arm, open-label study in refractory SAA subjects, showed consistent results. Data are limited to 21 out of the planned 60 patients with haematological responses reported by 52% of patients at 6 months. Multilineage responses were reported by 45% of patients.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Revolade in one or more subsets of the paediatric population in chronic idiopathic thrombocytopenic purpura (ITP) and Secondary Thrombocytopenia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Pharmacokinetics

The plasma eltrombopag concentration-time data collected in 88 patients with ITP in Studies TRA100773A and TRA100773B were combined with data from 111 healthy adult subjects in a population PK analysis. Plasma eltrombopag $AUC_{(0-\tau)}$ and Cmax estimates for ITP patients are presented (Table 7).

Table 7: Geometric mean (95 % confidence intervals) of steady-state plasma eltrombopag pharmacokinetic parameters in adults with ITP

Eltrombopag dose, once daily	N	$AUC_{(0-\tau)}$[a], µg.h/ml	C_{max}[a], µg/ml
30 mg	28	47 (39, 58)	3.78 (3.18, 4.49)
50 mg	34	108 (88, 134)	8.01 (6.73, 9.53)
75 mg	26	168 (143, 198)	12.7 (11.0, 14.5)

a - $AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates.

Plasma eltrombopag concentration-time data collected in 590 subjects with HCV enrolled in Phase III studies TPL103922/ENABLE 1 and TPL108390/ENABLE 2 were combined with data from patients with HCV enrolled in the Phase II study TPL102357 and healthy adult subjects in a population PK analysis. Plasma eltrombopag C_{max} $AUC_{(0-\tau)}$ estimates for patients with HCV enrolled in the Phase 3 studies are presented for each dose studied in Table 8.

Table 8 Geometric mean (95 % CI) steady-state plasma eltrombopag pharmacokinetic parameters in patients with chronic HCV

Eltrombopag dose (once daily)	**N**	**$AUC_{(0-\tau)}$ (µg.h/ml)**	**C_{max} (µg/ml)**
25 mg	330	118 (109, 128)	6.40 (5.97, 6.86)
50 mg	119	166 (143, 192)	9.08 (7.96, 10.35)
75 mg	45	301 (250, 363)	16.71 (14.26, 19.58)
100 mg	96	354 (304, 411)	19.19 (16.81, 21.91)

Data presented as geometric mean (95 % CI).
$AUC_{(0-\tau)}$ and C_{max} based on population PK post-hoc estimates at the highest dose in the data for each patient.

Absorption and bioavailability

Eltrombopag is absorbed with a peak concentration occurring 2 to 6 hours after oral administration. Administration of eltrombopag concomitantly with antacids and other products containing polyvalent cations such as dairy products and mineral supplements significantly reduces eltrombopag exposure (see section 4.2). The absolute oral bioavailability of eltrombopag after administration to humans has not been established. Based on urinary excretion and metabolites eliminated in faeces, the oral absorption of drug-related material following administration of a single 75 mg eltrombopag solution dose was estimated to be at least 52 %.

Distribution

Eltrombopag is highly bound to human plasma proteins (> 99.9 %), predominantly to albumin. Eltrombopag is a substrate for BCRP, but is not a substrate for P-glycoprotein or OATP1B1.

Biotransformation

Eltrombopag is primarily metabolized through cleavage, oxidation and conjugation with glucuronic acid, glutathione, or cysteine. In a human radiolabel study, eltrombopag accounted for approximately 64 % of plasma radiocarbon $AUC_{0-\infty}$. Minor metabolites due to glucuronidation and oxidation were also detected. *In vitro* studies suggest that CYP1A2 and CYP2C8 are responsible for oxidative metabolism of eltrombopag. Uridine diphosphoglucuronyl transferase UGT1A1 and UGT1A3 are responsible for glucuronidation, and bacteria in the lower gastrointestinal tract may be responsible for the cleavage pathway.

Elimination

Absorbed eltrombopag is extensively metabolised. The predominant route of eltrombopag excretion is via faeces (59 %) with 31 % of the dose found in the urine as metabolites. Unchanged parent compound (eltrombopag) is not detected in urine. Unchanged eltrombopag excreted in faeces accounts for approximately 20 % of the dose. The plasma elimination half-life of eltrombopag is approximately 21-32 hours.

Pharmacokinetic interactions

Based on a human study with radiolabelled eltrombopag, glucuronidation plays a minor role in the metabolism of eltrombopag. Human liver microsome studies identified UGT1A1 and UGT1A3 as the enzymes responsible for eltrombopag glucuronidation. Eltrombopag was an inhibitor of a number of UGT enzymes *in vitro*. Clinically significant drug interactions involving glucuronidation are not anticipated due to limited contribution of individual UGT enzymes in the glucuronidation of eltrombopag.

Approximately 21 % of an eltrombopag dose could undergo oxidative metabolism. Human liver microsome studies identified CYP1A2 and CYP2C8 as the enzymes responsible for eltrombopag oxidation. Eltrombopag does not inhibit or induce CYP enzymes based on *in vitro* and *in vivo* data (see section 4.5).

In vitro studies demonstrate that eltrombopag is an inhibitor of the OATP1B1 transporter and an inhibitor of the BCRP transporter and eltrombopag increased exposure of the OATP1B1 and BCRP substrate rosuvastatin in a clinical drug interaction study (see section 4.5). In clinical studies with eltrombopag, a dose reduction of statins by 50 % was recommended.

Eltrombopag chelates with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc (see sections 4.2 and 4.5).

Administration of a single 50 mg dose of eltrombopag with a standard high-calorie, high-fat breakfast that included dairy products reduced plasma eltrombopag $AUC_{(0-\infty)}$ and C_{max}. Whereas, low-calcium food [< 50 mg calcium] did not significantly impact plasma eltrombopag exposure, regardless of calorie and fat content (see sections 4.2 and 4.5).

Special patient populations

Renal impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with renal impairment. Following administration of a single 50 mg-dose, the $AUC_{0-\infty}$ of eltrombopag was 32 % to 36 % lower in subjects with mild to moderate renal impairment, and 60 % lower in subjects with severe renal impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with renal impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured. Patients with impaired renal function should use eltrombopag with caution and close monitoring, for example by testing serum creatinine and/or urine analysis (see section 4.2). The efficacy and safety of eltrombopag has not been established in subjects with both moderate to severe renal impairment and hepatic impairment.

Hepatic impairment

The pharmacokinetics of eltrombopag has been studied after administration of eltrombopag to adult subjects with hepatic impairment. Following the administration of a single 50 mg dose, the $AUC_{0-\infty}$ of eltrombopag was 41 % higher in subjects with mild hepatic impairment and 80 % to 93 % higher in subjects with moderate to severe hepatic impairment compared with healthy volunteers. There was substantial variability and significant overlap in exposures between patients with hepatic impairment and healthy volunteers. Unbound eltrombopag (active) concentrations for this highly protein bound medicinal product were not measured.

The influence of hepatic impairment on the pharmacokinetics of eltrombopag following repeat administration was evaluated using a population pharmacokinetic analysis in 28 healthy adults and 714 patients with hepatic impairment (673 patients with HCV and 41 patients with chronic liver disease of other aetiology). Of the 714 patients, 642 were with mild hepatic impairment, 67 with moderate hepatic impairment, and 2 with severe hepatic impairment. Compared to healthy volunteers, patients with mild hepatic impairment had approximately 111 % (95 % CI: 45 % to 283 %) higher plasma eltrombopag $AUC_{(0-\tau)}$ values and patients with moderate hepatic impairment had approximately 183 % (95 % CI: 90 % to 459 %) higher plasma eltrombopag $AUC_{(0-\tau)}$ values.

Therefore, eltrombopag should not be used in ITP patients with hepatic impairment (Child-Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis (see sections 4.2 and 4.4). For patients with HCV initiate eltrombopag at a dose of 25 mg once daily (see section 4.2).

Race

The influence of East Asian ethnicity on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (31 East Asians) and 88 patients with ITP (18 East Asians). Based on estimates from the population pharmacokinetic analysis, East Asian (i.e. Japanese, Chinese, Taiwanese and Korean) ITP patients had approximately 87 % higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to non-East Asian patients who were predominantly Caucasian, without adjustment for body weight differences (see section 4.2).

The influence of East Asian ethnicity (such as Chinese, Japanese, Taiwanese, Korean, and Thai) on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 635 patients with HCV (145 East Asians and 69 Southeast Asians). Based on estimates from the population pharmacokinetic analysis, East Asian patients had approximately 55 % higher plasma eltrombopag $AUC_{(0-\tau)}$ values as compared to patients of other races who were predominantly Caucasian (see section 4.2).

Gender

The influence of gender on the pharmacokinetics of eltrombopag was evaluated using a population pharmacokinetic analysis in 111 healthy adults (14 females) and 88 patients with ITP (57 females). Based on estimates from the population pharmacokinetic analysis, female ITP patients had approximately 50 % higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients, without adjustment for body weight differences.

The influence of gender on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 635 patients with HCV (260 females). Based on model estimate, female HCV patient had approximately 41 % higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to male patients.

Age

The influence of age on eltrombopag pharmacokinetics was evaluated using population pharmacokinetics analysis in 28 healthy subjects, 673 patients with HCV, and 41 patients with chronic liver disease of other aetiology ranging from 19 to 74 years old. There are no PK data on the use of eltrombopag in patients ≥ 75 years. Based on model estimate, elderly (≥ 65 years) patients had approximately 41 % higher plasma eltrombopag $AUC_{(0-\tau)}$ as compared to younger patients (see section 4.2).

5.3 Preclinical safety data

Eltrombopag does not stimulate platelet production in mice, rats or dogs because of unique TPO receptor specificity. Therefore, data from these animals do not fully model potential adverse effects related to the pharmacology of eltrombopag in humans, including the reproduction and carcinogenicity studies.

Treatment-related cataracts were detected in rodents and were dose and time-dependent. At ≥ 6 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 6 weeks and rats after 28 weeks of dosing. At ≥ 4 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human exposure in HCV patients at 100 mg/day, based on AUC, cataracts were observed in mice after 13 weeks and in rats after 39 weeks of dosing. Cataracts have not been observed in dogs after 52 weeks of dosing at 2 times the human clinical exposure in ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC).

Renal tubular toxicity was observed in studies of up to 14 days duration in mice and rats at exposures that were generally associated with morbidity and mortality. Tubular toxicity was also observed in a 2 year oral carcinogenicity study in mice at doses of 25, 75 and 150 mg/kg/day. Effects were less severe at lower doses and were characterized by a spectrum of regenerative changes. The exposure at the lowest dose was 1.2 times the human clinical exposure based on AUC in ITP patients at 75 mg/day and 0.6 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC. Renal effects were not observed in rats after 28 weeks or in dogs after 52 weeks at exposures 4 and 2 times the human clinical exposure in ITP patients at 75 mg/day and 2 times and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Hepatocyte degeneration and/or necrosis, often accompanied by increased serum liver enzymes, was observed in mice, rats and dogs at doses that were associated with morbidity and mortality or were poorly tolerated. No hepatic effects were observed after chronic dosing in rats (28 weeks) and in dogs (52 weeks) at 4 or 2 times the human clinical exposure in ITP patients at 75 mg/day and 2 times and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

At poorly tolerated doses in rats and dogs (> 10 times the human clinical exposure in ITP patients at 75 mg/day and> 4 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC), decreased reticulocyte counts and regenerative bone marrow erythroid hyperplasia (rats only) were observed in short term studies. There were no effects of note on red cell mass or reticulocyte counts after dosing for up to 28 weeks in rats, 52 weeks in dogs and 2 years in mice or rats at maximally tolerated doses which were 2 to 4 times human clinical exposure in ITP patients at 75 mg/day and ≤ 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Endosteal hyperostosis was observed in a 28 week toxicity study in rats at a non-tolerated dose of 60 mg/kg/day (6 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). There were no bone changes observed in mice or rats after lifetime exposure (2 years) at 4 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC.

Eltrombopag was not carcinogenic in mice at doses up to 75 mg/kg/day or in rats at doses up to 40 mg/kg/day (exposures up to 4 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Eltrombopag was not mutagenic or clastogenic in a bacterial mutation assay or in two in vivo assays in rats (micronucleus and unscheduled DNA synthesis, 10 times the human clinical exposure in ITP patients at 75 mg/day and 7 times the human clinical exposure in HCV patients at 100 mg/day, based on C_{max}). In the *in vitro* mouse lymphoma assay, eltrombopag was marginally positive (< 3-fold increase in mutation frequency). These *in vitro* and *in vivo* findings suggest that eltrombopag does not pose a genotoxic risk to humans.

Eltrombopag did not affect female fertility, early embryonic development or embryofoetal development in rats at doses up to 20 mg/kg/day (2 times the human clinical exposure in ITP patients at 75 mg/day and equivalent to the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Also there was no effect on embryofoetal development in rabbits at doses up to 150 mg/kg/day, the highest dose tested (0.3 to 0.5 times the human clinical exposure in ITP patients at 75 mg/day and HCV Patients at 100 mg/day, based on AUC). However, at a maternally toxic dose of 60 mg/kg/day (6 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) in rats, eltrombopag treatment was associated with embryo lethality (increased pre- and post-implantation loss), reduced foetal body weight and gravid uterine weight in the female fertility study and a low incidence of cervical ribs and reduced foetal body weight in the embryofoetal development study. Eltrombopag should be used during pregnancy only if the expected benefit justifies the potential risk to the foetus (see section 4.6). Eltrombopag did not affect male fertility in rats at doses up to 40 mg/kg/day, the highest dose tested (3 times the human clinical exposure in ITP patients at 75 mg/day and 2 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). In the pre- and post-natal development study in rats, there were no undesirable effects on pregnancy, parturition or lactation of F_0 female rats at maternally non-toxic doses (10 and 20 mg/kg/day) and no effects on the growth, development, neurobehavioral or reproductive function of the offspring (F_1). Eltrombopag was detected in the plasma of all F_1 rat pups for the entire 22 hour sampling period following administration of medicinal product to the F_0 dams, suggesting that rat pup exposure to eltrombopag was likely via lactation.

In vitro studies with eltrombopag suggest a potential phototoxicity risk; however, in rodents there was no evidence of cutaneous phototoxicity (10 times the human clinical exposure in ITP patients at 75 mg/day and 5 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC) or ocular phototoxicity (≥ 5 times the human clinical exposure in ITP patients at 75 mg/day and 3 times the human clinical exposure in HCV patients at 100 mg/day, based on AUC). Furthermore, a clinical pharmacology study in 36 subjects showed no evidence that photosensitivity was increased following administration of eltrombopag 75 mg. This was measured by delayed phototoxic index. Nevertheless, a potential risk of photoallergy cannot be ruled out since no specific preclinical study could be performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Magnesium stearate
Mannitol (E421)
Microcrystalline cellulose
Povidone (K30)
Sodium starch glycolate Type A

Tablet coating
Hypromellose
Iron oxide red (E172)
Iron oxide black (E172)
Macrogol 400
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminum blisters (PA/Alu/PVC/Alu) in a carton containing 14 or 28 film-coated tablets and multipacks containing 84 (3 packs of 28) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/007
EU/1/10/612/008
EU/1/10/612/009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 March 2010
Date of the latest renewal: 15 January 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations)
Priory Street
Ware, Herts SG12 0DJ
United Kingdom

Glaxo Wellcome S.A.
Avenida de Extremadura 3
09400 Aranda de Duero
Burgos
Spain

Novartis Pharmaceuticals UK Limited
Frimley Business Park
Frimley
Camberley, Surrey GU16 7SR
United Kingdom

Novartis Pharma GmbH
Roonstraße 25
D-90429 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription. (see Annex I: Summary of Product Characteristics, 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall agree the details of an educational programme with the National Competent Authorities and must implement such programme nationally to ensure that, prior to prescribing all physicians are provided with a healthcare professional information pack containing the following:

- Educational material
- Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling

Key elements to be included in the educational material

Hepatotoxicity

• Educate patients about the potential for hepatic enzyme elevations, importance of monthly laboratory monitoring of ALT and AST, as well as the signs and symptoms associated with liver injury (e.g. jaundice).
• Measure serum ALT, AST and bilirubin prior to initiation of Revolade, every 2 weeks during the dose adjustment phase and monthly following establishment of a stable dose.
• Discontinue Revolade if ALT levels increase (≥ 3X the upper limit of normal [ULN]) and are:
- progressive, or
- persistent for > 4 weeks, or
- accompanied by increased direct bilirubin, or
- accompanied by clinical symptoms of liver injury or evidence for hepatic decompensation.
• Exercise caution when administering eltrombopag to patients with hepatic disease. Use a lower starting dose of eltrombopag and monitor closely when administering eltrombopag to patients with hepatic impairment.

Thromboembolic events
ITP patients

• Eltrombopag should not be used in patients with hepatic impairment (Child Pugh score ≥ 5) unless the expected benefit outweighs the identified risk of portal venous thrombosis. If use of eltrombopag is deemed necessary, the starting dose must be 25 mg once daily.
• Educate patients about the potential for thromboembolic events (TEE) in patients with chronic ITP and those known risk factors for thromboembolic events (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome).
• Educate patients about chronic liver disease and the risk of thromboembolic events.
• In patients with chronic liver disease treated with eltrombopag there was an association between TEE and platelet counts ≥ 200,000µl.
• A dose reduction is recommended for ITP patients with platelet counts between 150,000-250,000/µl.
• Revolade should be interrupted if platelet counts increase to > 250,000/µl. Once the platelet count is < 100,000/µl, reinitiate therapy at a reduced daily dose.

HCV patients

- Thrombocytopenic patients with HCV should initiate eltrombopag at a dose of 25 mg once daily.
- Educate thrombocytopenic patients with chronic HCV about the risk of thromboembolic events, particularly the increased incidence of portal vein thrombosis and known risk factors for thromboembolic events (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome).
- In thrombocytopenic patients with chronic HCV there was no specific temporal relationship between start of treatment and event of TEE. TEEs were more common in patients > 60 years old and in patients with albumin below 35 g/L.
- A dose reduction is recommended for thrombocytopenic chronic HCV patients with platelet counts between 100,000-150,000/µl.
- Revolade should be interrupted if platelet counts increase to > 150,000/µl. Once the platelet count is < 100,000/µl, reinitiate therapy at a reduced daily dose.

Posology

• Educate patients on the appropriate administration of Revolade (e.g. titration of Revolade, food-medicinal product interaction, dose recommendations for special populations [e.g. East Asians]).

Food Interactions

• Educate patients about the potential food-medicinal product interaction (i.e. chelation with polyvalent cations such as iron, calcium, magnesium, aluminium, selenium and zinc). Antacids, dairy products and other products containing polyvalent cations, such as mineral supplements, must be administered at least four hours apart from Revolade dosing to avoid significant reduction in Revolade absorption due to chelation.
• Assist patient in developing a plan to administer Revolade at a time each day that fits into the patient's own daily schedule.

Reoccurrence of Thrombocytopenia

• Educate patients about the potential risk of bleeding after treatment has stopped (include incidence in clinical trials and likelihood of reoccurrence of thrombocytopenia after cessation of treatment).
• Following discontinuation of Revolade, platelet counts return to baseline levels within 2 weeks in the majority of patients, which increase the bleeding risk and in some cases may lead to bleeding.
• Monitor platelet count weekly for 4 weeks following discontinuation of Revolade.

Increased Bone Marrow Reticulin Fibres

• Educate patients about the potential for bone marrow reticulin fibre formation.
• Background information on reticulin in the bone marrow (i.e. background rates of reticulin in bone marrow in ITP patients and the observed incidence and potential mechanism of action of reticulin deposition in response to Revolade).
• Prior to initiation of Revolade, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities.
• Following identification of a stable dose of Revolade, perform full blood count (FBC) with white blood cell count (WBC) differential monthly.
• If immature or dysplastic cells are observed, examine peripheral blood smears for new or worsening morphological abnormalities (e.g., teardrop and nucleated red blood cells, immature white blood cells) or cytopenia(s).
• If the patient develops new or worsening morphological abnormalities or cytopenia(s), discontinue treatment with Revolade and consider a bone marrow biopsy, including staining for fibrosis.

Haematological malignancies

• The diagnosis of ITP in adults and elderly patients should have been confirmed by excluding other clinical entities with thrombocytopenia. Consideration should be given to performing a bone marrow aspirate and biopsy over the course of the disease and treatment, particularly in patients over 60 years of age, those with systemic symptoms or abnormal signs.
• Educate patients about the theoretical risk of haematological malignancies with thrombopoietin receptor agonists.
• Importance of not using Revolade outside the context of its license unless in a clinical trial setting.

Potential for Off-label Use

• The risk-benefit for the treatment of thrombocytopenia outside of the registered indication has not been established.
• The risk-benefit of Revolade in paediatric ITP and paediatric HCV-associated thrombocytopenia has not been established. The paediatric population is defined as those persons aged between 0 and 18 years.
• Awareness to prescribers of the labelled indication and warnings associated with non-indicated populations (e.g. not recommended for use in children, pregnant or breast-feeding women, other off label uses).

Hepatic Decompensation (use with interferon)

- Chronic HCV patients with cirrhosis may be at risk of hepatic decompensation when receiving alfa-interferon therapy
- Educate thrombocytopenic patients with chronic HCV that safety findings suggestive of hepatic decompensation were reported more frequently in patients treated with eltrombopag/interferon/ribavirin.
- Thrombocytopenic patients with chronic HCV with low albumin (≤ 35 g/L) or Model for End-Stage Liver Disease (MELD) score ≥ 10 at baseline had a greater risk of hepatic decompensation when treated with eltrombopag/interferon/ribavirin. Patients with these signs should be closely monitored for signs and symptoms of hepatic decompensation.

Fatal Adverse Reactions in thrombocytopenic patients with HCV

- In thrombocytopenic patients with chronic HCV, patients who receive anti viral therapy in combination with eltrombopag may be at greater risk of fatal adverse reactions, particularly those with the poorest prognosis, i.e.:
  - MELD score ≥10,
  - Albumin ≤ 35 g/L
- Educate patients with the poorest prognosis about the increased risk of fatal adverse reactions, particularly hepatic decompensation (hepatic failure, ascites, encephalopathy and bleeding varices), infective and ischemic complications.
- Treatment with eltrombopag should be stopped if signs and symptoms suggestive of thrombotic events and hepatic decompensation occur (see TEE and hepatic decompensation above).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF 25 mg 50 mg 75 mg **– 14, 28, 84 (3 PACKS of 28) TABLETS**

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg film-coated tablets
Revolade 50 mg film-coated tablets
Revolade 75 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.
Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag
Each film-coated tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
28 film-coated tablets
Multipack containing 84 (3 packs of 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/001 (14 film-coated tablets)
EU/1/10/612/002 (28 film-coated tablets)
EU/1/10/612/003 84 film-coated tablets (3 packs of 28)
EU/1/10/612/004 (14 film-coated tablets)
EU/1/10/612/005 (28 film-coated tablets)
EU/1/10/612/006 84 film-coated tablets (3 packs of 28)
EU/1/10/612/007 (14 film-coated tablets)
EU/1/10/612/008 (28 film-coated tablets)
EU/1/10/612/009 84 film-coated tablets (3 packs of 28)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 25 mg
revolade 50 mg
revolade 75 mg

PARTICULARS TO APPEAR ON INTERMEDIATE CARTON

Multipacks of 84 (3 packs of 28 film-coated tablets) – without blue box – 25 mg 50 mg 75 mg **film-coated tablets**

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg film-coated tablets
Revolade 50 mg film-coated tablets
Revolade 75 mg film-coated tablets

eltrombopag

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.
Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag
Each film-coated tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/612/003
EU/1/10/612/006
EU/1/10/612/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

revolade 25 mg
revolade 50 mg
revolade 75 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE MEDICINAL PRODUCT

Revolade 25 mg film-coated tablets
Revolade 50 mg film-coated tablets
Revolade 75 mg film-coated tablets

eltrombopag

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the patient

Revolade 25 mg film-coated tablets
Revolade 50 mg film-coated tablets
Revolade 75 mg film-coated tablets

eltrombopag

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4

What is in this leaflet:

1. What Revolade is and what it is used for
2. What you need to know before you take Revolade
3. How to take Revolade
4. Possible side effects
5. How to store Revolade
6. Contents of the pack and other information

1. What Revolade is and what it is used for

Eltrombopag the active substance in Revolade belongs to a group of medicines called thrombopoietin receptor agonists. It is used to help increase the number of platelets in your blood. Platelets are blood cells that help to reduce or prevent bleeding.

Revolade may be used to treat a bleeding disorder called immune (idiopathic) thrombocytopenic purpura (ITP) in adult patients (aged 18 years and over) who have had their spleen removed and have received prior treatment with corticosteroids or immunoglobulins, and these medicines did not work. ITP is caused by a low blood platelet count (thrombocytopenia). People with ITP have an increased risk of bleeding. Symptoms patients with ITP may notice include petechiae (pinpoint sized flat round red spots under the skin), bruising, nosebleeds, bleeding gums and not being able to control bleeding if they are cut or injured.

Revolade may also be used in previously treated adult patients (aged 18 years and over) with chronic ITP when surgery to remove the spleen is not an option.

Revolade may also be used to treat low platelet count (thrombocytopenia) in adult patients with chronic hepatitis C virus (HCV) infections, where the severity of the thrombocytopenia is the main factor that prevents starting or maintaining the proper dose of interferon-based treatment. People with HCV infections may have low platelet counts, not only as a result of the disease, but also due to some of the antiviral medicines that are used to treat it.

Revolade may also be used to treat adult patients with low blood counts caused by severe aplastic anaemia (SAA).

2. What you need to know before you take Revolade

Don’t take Revolade

- **if you are allergic** to eltrombopag or any of the other ingredients of this medicine (listed in section 6 under ‘What Revolade contains’).
  - **Check with your doctor** if you think this applies to you.

Warnings and precautions

Your doctor needs to know before you take Revolade:

- if you have **liver problems.**
  - There is an increased risk for side effects, including potentially fatal liver problems and blood clots, in patients with low platelet counts (thrombocytopenic) and advanced chronic liver disease, a long-standing or recurring disorder resulting in liver damage reducing the functioning of the liver. If your doctor considers that the benefits outweigh the risks, you will be closely monitored during your treatment.
- if you are at risk of **blood clots** in your veins or arteries, or you know that blood clots are common in your family.
  - You may be at **higher risk of blood clots**:
    - as you get older
    - if you have had to stay in bed for a long time
    - if you have cancer
    - if you are taking the contraceptive birth control pill or hormone replacement therapy
    - if you have recently had surgery or received a physical injury
    - if you are very overweight (obese)
    - if you are a smoker
    - if you have advanced chronic liver disease
  - If any of these apply to you **tell your doctor** before starting treatment. You should not take Revolade unless your doctor considers that the expected benefits outweigh the risk of blood clots.
- if you have **cataracts** (the lens of the eye getting cloudy)
- if you have another **blood condition**, such as myelodysplastic syndrome (MDS). Your doctor will carry out tests to check that you do not have this blood condition before you start Revolade. If you have MDS and take Revolade, your MDS may get worse.
  - Tell your doctor if any of these apply to you.

Eye examinations

Your doctor will recommend that you are checked for cataracts as part of routine eye tests. If you do not have routine eye-tests your doctor should arrange regular testing to check for cataracts. You may also be checked for the occurrence of any bleeding from the blood vessels in or around your retina (the light sensitive layer of cells at the back of the eye).

You will need regular blood tests

Before you start taking Revolade your doctor will carry out blood tests to check your blood cells, including platelets. These tests will be repeated at intervals while you are taking it.

Blood tests for liver function
Revolade can cause an increase of some liver enzymes in the blood, especially bilirubin and alanine / aspartate transaminases. This may be a sign that the liver is being damaged. If you are taking interferon based antiviral treatments together with Revolade to treat low platelet count due to hepatitis C virus (HCV) infections, some liver problems can get worse.

You will have blood tests to check your liver function before you start taking Revolade and at intervals while you are taking it. You may need to stop taking Revolade if the amount of these substances increases too much, or if you get physical signs of liver damage.

- **Read the information 'Problems with your liver' in section 4 of this leaflet.**

Blood tests for platelet count
If you stop taking Revolade, your blood platelet count is likely to become low again within several days. Your platelet count will be monitored, and your doctor will discuss appropriate precautions with you.

If you have a very high blood platelet count, this may increase the risk of blood clotting. However blood clots can occur with normal or even low platelet counts. Your doctor will adjust your dose of Revolade to ensure that your platelet count does not become too high.

Get medical help immediately if you have any of these signs of a blood clot:
- **swelling**, **pain** or tenderness in **one leg**
- **sudden shortness of breath** especially together with sharp pain in the chest or rapid breathing
- abdominal (stomach) pain, enlarged abdomen, blood in your stools

Tests to check your bone marrow
Some people may have problems with their bone marrow. Medicines like Revolade could make this problem worse. Signs of bone marrow changes may show up as abnormal results in your blood tests. Your doctor may also carry out tests to directly check your bone marrow during treatment with Revolade.

Checks for digestive bleeding
If you are taking interferon based antiviral treatments together with Revolade you will be monitored for any signs or symptoms of gastrointestinal bleeding after discontinuation of Revolade.

Heart monitoring
Your doctor may consider it necessary to monitor your heart during treatment with Revolade and consider performing an electrocardiogram test.

Children and adolescents
Revolade is not recommended for people aged under 18 years

Other medicines and Revolade
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Some everyday medicines interact with Revolade – including prescription and non-prescription medicines and minerals. These include:

- antacid medicines to treat **indigestion**, **heartburn** or **stomach ulcers** *(*see also section 3)
- medicines called statins, to **lower cholesterol**
- some medicines to treat **HIV infection**, such as lopinavir or ritonavir
- minerals such as iron, calcium, magnesium, aluminium, selenium and zinc which may be found in **vitamin and mineral supplements** (see also section 3)
- medicines such as methotrexate and topotecan, to treat **cancer**

  - **Talk to your doctor** if you take any of these. Some of them are not to be taken with Revolade,, or your dose may need adjusting, or you may need to alter the timing of when you take them. Your doctor will review the medicines you are taking, and suggest suitable replacements if necessary.

If you are also taking medicines to prevent blood clots (anticoagulants or antiplatelet therapy) there is a greater risk of bleeding. Your doctor will discuss this with you.

If you are taking corticosteroids, danazol, and/or azathioprine you may need to take a lower dose or to stop taking them while you are taking Revolade.

Revolade with food and drink
Do not take Revolade with dairy foods or drinks as the absorption of the medicine is affected by the calcium in dairy products. For more information, see section 3, '***How to take Revolade****'*.

Pregnancy and breast-feeding
Don't use Revolade if you are pregnant unless your doctor specifically recommends it. The effect of Revolade during pregnancy is not known.

- **Tell your doctor if you are pregnant,** think you may be pregnant, or are planning to have a baby.
- **Use a reliable method of contraception** while you're taking Revolade, to prevent pregnancy
- **If you do become pregnant during treatment** with Revolade, tell your doctor.

Don't breast-feed while you are taking Revolade. It is not known whether Revolade passes into breast-milk.

- **If you are breast-feeding** or planning to breast-feed, tell your doctor.

Driving and using machines
Revolade can make you dizzy and have other side effects that make you less alert.

- **Don't drive or use machines** unless you are sure you're not affected.

3. How to take Revolade

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Do not change your dose or schedule for taking Revolade unless your doctor or pharmacist tells you to change it. When you receive Revolade you will be under the supervision of a physician who is experienced in the treatment of haematological disease or the management of chronic hepatitis C.

How much to take
The usual starting dose for people with ITP and SAA is **one 50 mg tablet** of Revolade once a day. If you are of east asian origin (Chinese, Japanese, Taiwanese, Thai or Korean) you may need to start at a **lower dose of 25 mg.**

The usual starting dose for people with hepatitis C is **one 25 mg tablet** of Revolade once a day. If you are of east asian origin (Chinese, Japanese, Taiwanese, Thai or Korean) you will start on the **same 25 mg dose.**

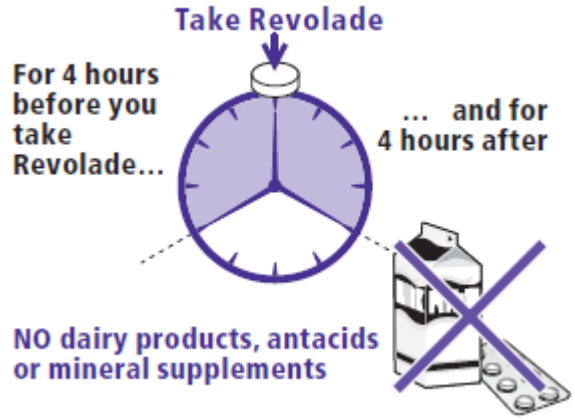
The aim of treatment with Revolade for people with hepatitis C is to achieve the platelet counts needed to start and during treatment with anti-viral therapy.

Swallow the tablet whole, with some water.

Revolade may take 1 to 2 weeks to work. Based on your response to Revolade your doctor may recommend that your daily dose is changed.

When to take it
Don't take Revolade in the **4 hours** before or after:
- **dairy foods** such as cheese, butter, yoghurt or ice cream
- **milk or milk shakes,** drinks containing milk, yoghurt or cream
- **antacids,** a type of medicine for **indigestion and heartburn**
- some **mineral and vitamin supplements** including iron, calcium, magnesium, aluminium, selenium and zinc

If you do, the medicine will not be properly absorbed into your body.



For more advice about suitable foods and drinks, talk to your doctor.

If you take more Revolade than you should

Contact a doctor or pharmacist immediately. If possible show them the pack, or this leaflet. You will be monitored for any signs or symptoms of side effects and given appropriate treatment immediately.

If you forget to take Revolade
If you miss a dose of Revolade, wait and take your next scheduled dose. Do not take more than one dose of Revolade in one day.

If you stop taking Revolade
Don't stop taking Revolade without talking to your doctor. If your doctor advises you to stop treatment, your platelet count will then be checked each week for four weeks.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Symptoms needing attention: see a doctor
People taking Revolade for either ITP or low blood platelet counts due to chronic hepatitis C infection could develop signs of potentially serious side effects. **It is important to tell a doctor if you develop the following symptoms**.

Higher risk of blood clots
Certain people may have a higher risk of blood clots, and medicines like Revolade could make this problem worse. The sudden blocking of a blood vessel by a blood clot is an uncommon side effect and may affect up to 1 in 100 people.

If you develop signs and symptoms of a blood clot, such as:
- **swelling, pain** or tenderness in **one leg**
- **sudden shortness of breath**, especially together with sharp pain in the chest or rapid breathing
- abdominal (stomach) pain, enlarged abdomen, blood in your stools.

Get medical help immediately.

Problems with your liver
Revolade can cause changes that show up in blood tests, and may be signs of liver damage. Liver problems occur commonly and may affect up to 1 in 10 people. Liver problems including: increased level of substances (enzymes) produced by the liver, bile produced by liver to aid digestion of food not flowing properly (cholestasis) occur uncommonly and may affect up to 1 in 100 people.

➔ **Tell your doctor immediately** if you have any of these signs and symptoms of liver problems:
- Yellowing of the skin or the whites of the eyes (jaundice)
- Unusually dark-coloured urine

Bleeding or bruising after you stop treatment
Within two weeks of stopping Revolade, your blood platelet count will usually drop back down to what it was before you started taking Revolade. The lower platelet count may increase your risk of bleeding or bruising. Your doctor will check your platelet counts for at least 4 weeks after you stop taking Revolade.

Some people may have problems with bleeding in the digestive system following discontinuation of peginterferon, ribavirin, and Revolade. Contact your doctor if:
- You have black tarry stools (This may be a sign of GI bleeding, discoloured bowel movements are a uncommon side effect that may affect up to 1 in 100 people)
- You have blood in your stool
- You vomit blood or you vomit material that looks like coffee grounds

➔ **Tell your doctor** if you have any bruising or bleeding after you stop taking Revolade.

Other possible side effects in people with ITP

Common side effects
These may affect **up to 1 in 10** people:
- feeling sick (nausea)
- diarrhoea
- cloudy lens in the eye (cataract)
- dry eyes
- unusual hair loss or thinning
- skin rash
- itching
- muscle pain, muscle spasm

- back pain
- bone pain
- tingling or numbness of the hands or feet
- heavy menstrual cycle or period
- mouth ulcers

Common side effects that may show up in blood tests:
- increase of liver enzymes (aspartate and alanine transaminases)
- increase in *bilirubin* (a substance produced by the liver)
- increased levels of some proteins

Uncommon side effects
These may affect **up to 1 in 100** people:
- interruption of blood supply to part of the heart, heart attack
- sudden shortness of breath, especially when accompanied with sharp pain in the chest and /or rapid breathing, which could be signs of a blood clot in the lungs
- the loss of function of part of the lung caused by a blockage in the lung artery
- heart beating faster, irregular heartbeat, bluish discolouration of the skin
- disturbances of heart rhythm (QT prolongation)
- inflammation of a vein
- localised swelling filled with blood from a break in a blood vessel (haematoma)
- sore throat and discomfort when swallowing, inflammation of the lungs, sinuses, tonsils, nose and throat
- flu (influenza)
- pneumonia
- loss of appetite
- painful swollen joints caused by uric acid (gout)
- problems sleeping, depression, lack of interest, mood changes
- feeling drowsy, problems with balance speech and nerve function, migraine, shaking
- eye problems, including blurred and less clear vision
- ear pain, spinning sensation (vertigo)
- problems with the nose, throat and sinuses, breathing problems when sleeping
- digestive system problems including: being sick (vomiting), wind, frequent bowel movements, stomach pain and tenderness
- food poisoning
- cancer of the rectum
- mouth problems, including dry or sore mouth sensitive tongue, bleeding gums
- skin changes including, excessive sweating, itching bumpy rash, red spots, changes in appearance
- sunburn
- redness or swelling around a wound
- bleeding around a catheter into the skin
- sensation of a foreign body
- muscular weakness
- kidney problems including: inflammation of the kidney, excessive urination at night, kidney failure, urinary tract infection
- white cells in urine
- generally feeling unwell (malaise), high temperature, feeling hot, chest pain
- cold sweat
- inflammation of the gum tissue
- infection of skin

Uncommon side effects that may show up in blood tests:
- decreased number of red blood cells (anaemia), white blood cells and platelets
- increased number of red blood cells
- changes in the make-up of the blood
- changes in levels of uric acid, calcium and potassium

Other possible side effects in people with hepatitis C (taking Revolade with, peginterferon and ribavirin)

Very common side effects
These may affect **more than 1 in 10** people:
- headache
- decreased appetite
- difficulty in sleeping (insomnia)
- cough
- feeling sick (nausea), diarrhoea
- muscle pain, itching, lack of energy, high temperature, unusual hair loss, feeling weak, flu like illness, swelling in the hands or feet, chills

Very common side effects that may show up in blood tests:
- decreased number of red blood cells (anaemia).

Common side effects
These may affect **up to 1 in 10** people:
- infection of the urinary system
- inflammation of the nasal passages, throat and mouth, flu-like symptoms, dry mouth, sore or inflamed mouth, toothache
- weight loss
- sleep disorders, abnormal drowsiness, confusion, depression, anxiety, agitation
- dizziness, problems with attention and memory,
- tingling or numbness of the hands or feet
- inflammation in the brain
- eye problems, including: cloudy lens in the eye (cataract), dry eye, small yellow deposits in the retina, yellowing of the whites of the eye
- bleeding in the blood vessels in or around the retina (membrane in the back of the eye)
- spinning sensation, fast or irregular heartbeat (palpitations), shortness of breath
- cough bringing up phlegm
- digestive system problems, including: being sick (vomiting), stomach pain, indigestion, constipation, swollen stomach, taste disturbances, inflammation of the stomach, piles (haemorrhoids), swollen blood vessels and bleeding in the gullet (oesophagus), irritation of the gut
- liver problems, including blood clot, yellowing of the whites of the eye or skin (jaundice), tumour in the liver *(see '**Problems with your liver**' earlier in section 4)*
- skin changes, including: rash, dry skin, eczema, redness of the skin, itching, excessive sweating, unusual skin growths
- joint pain, back pain, bone pain, pain in the hands or feet, muscle spasms
- irritability, generally feeling unwell, chest pain and discomfort
- injection site reaction
- disturbances of heart rhythm (QT prolongation)

Common side effects that may show up in blood tests:
- increased blood sugar (glucose)
- reduced number of white blood cells
- reduced blood proteins
- breakdown of red blood cells (haemolytic anaemia)
- increased bilirubin (a substance produced by the liver)
- changes in the enzymes that control blood clotting

Uncommon side effects
These may affect **up to 1 in 100** people:
- pain when passing urine

The following side effects have been reported to be associated with treatment with Revolade in patients with severe aplastic anaemia (SAA).

Very common side effects
These may affect more than 1 in 10 people.
- cough
- headache
- shortness of breath (*dyspnoea*)
- pain in the nose and throat
- runny nose (*rhinorrhoea)*
- abdominal pain
- diarrhoea
- nausea
- bruising (*ecchymosis*)
- joint pain (*arthralgia*)
- muscle spasms
- pain in extremities (*arms, legs, hands and feet*)
- dizziness
- feeling very tired (*fatigue*)
- fever
- inability to sleep (*insomnia*)

Very common side effects that may show up in the blood tests
- increase in some liver enzymes (*transaminases*)

Laboratory tests may show abnormal changes to the cells in your bone marrow.

Common side effects
These may affect up to 1 in 10 people.
- anxiety
- depression
- feeling cold
- feeling unwell
- eye problems including: blurred and less clear vision, cloudy lens in the eye (*cataract*), spots or deposits in eye (vitreous floaters), dry eye, itchy eye, yellowing of the whites of the eye or skin
- nose bleed (*epistaxis*)
- bleeding of the gums
- blisters in the mouth
- digestive system problems including: being sick (vomiting), change in appetite (increased or decreased) stomach pain/discomfort, swollen stomach, passing wind, change in stool colour
- fainting
- skin problems including:Small red or purple spot caused by bleeding into the skin (*petechiae*) rash, itching, skin lesion

- back pain
- muscle pain
- bone pain
- weakness (*asthenia*)
- swelling of tissues, usually in the lower limbs, due to the accumulation of fluids
- abnormal colored urine
- interruption in blood supply to spleen (splenic infarction)

C**ommon side effects that may show up in the blood tests**
- increase in enzymes due to muscle breakdown (*creatine phoshokinase)*
- accumulation of iron in the body (*iron overload*)
- decreased number of white blood cells (neutropenia)
- decrease in sugar level (hypoglycemia)
- increased bilirubin (a substance produced by the liver)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Revolade

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Revolade contains

25 mg film-coated tablets

The active substance in Revolade is eltrombopag. Each film-coated tablet contains eltrombopag olamine equivalent to 25 mg eltrombopag.

The other ingredients are: hypromellose, macrogol 400, magnesium stearate, mannitol (E421), microcrystalline cellulose, polysorbate 80, povidone (K30), sodium starch glycolate Type A titanium dioxide (E171).

50 mg film-coated tablets

The active substance in Revolade is eltrombopag. Each film-coated tablet contains eltrombopag olamine equivalent to 50 mg eltrombopag.

The other ingredients are: hypromellose, iron oxide red (E172), iron oxide yellow (E172), macrogol 400, magnesium stearate, mannitol (E421), microcrystalline cellulose, povidone (K30), sodium starch glycolate Type A, titanium dioxide (E171).

75 mg film-coated tablets

The active substance in Revolade is eltrombopag. Each film-coated tablet contains eltrombopag olamine equivalent to 75 mg eltrombopag.

The other ingredients are: hypromellose, iron oxide red (E172), iron oxide black (E172), macrogol 400, magnesium stearate, mannitol (E421), microcrystalline cellulose, povidone (K30), sodium starch glycolate Type A, titanium dioxide (E171).

What Revolade looks like and contents of the pack

Revolade 25 mg film-coated tablets are round, biconvex, white, debossed with 'GS NX3' and '25' on one side.

Revolade 50 mg film-coated tablets are round, biconvex, brown, debossed with 'GS UFU' and '50' on one side.

Revolade 75 mg film-coated tablets are round, biconvex, pink, debossed with 'GS FFS' and '75' on one side.

They are supplied in aluminum blisters in a carton containing 14 or 28 film-coated tablets and multipacks containg 84 (3 packs of 28) film-coated tablets).

Not all pack sizes may be available in your country.

Marketing authorisation holder
Novartis Europharm Limited
Frimley Business Park
Camberley GU16 7SR
United Kingdom

Manufacturer
Glaxo Operations UK Ltd (trading as Glaxo Wellcome Operations), Priory Street, Ware, Hertfordshire, SG12 0DJ, United Kingdom
Glaxo Wellcome S.A., Avenida de Extremadura 3, 09400 Aranda de Duero, Burgos, Spain
Novartis Pharmaceuticals UK Limited, Frimley Business Park, Frimley, Camberley, Surrey GU16 7SR, United Kingdom
Novartis Pharma GmbH, Roonstraße 25, D-90429 Nuremberg, Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

България
Novartis Pharma Services Inc.
Тел: +359 2 489 98 28

Česká republika
Novartis s.r.o.
Tel: +420 225 775 111

Lietuva
Novartis Pharma Services Inc.
Tel: +370 5 269 16 50

Luxembourg/Luxemburg
Novartis Pharma N.V.
Tél/Tel: +32 2 246 16 11

Magyarország
Novartis Hungária Kft. Pharma
Tel.: +36 1 457 65 00

Danmark
Novartis Healthcare A/S
Tlf: +45 39 16 84 00

Deutschland
Novartis Pharma GmbH
Tel: +49 911 273 0

Eesti
Novartis Pharma Services Inc.
Tel: +372 66 30 810

Ελλάδα
Novartis (Hellas) A.E.B.E.
Τηλ: +30 210 281 17 12

España
Novartis Farmacéutica, S.A.
Tel: +34 93 306 42 00

France
Novartis Pharma S.A.S.
Tél: +33 1 55 47 66 00

Hrvatska
Novartis Hrvatska d.o.o.
Tel. +385 1 6274 220

Ireland
Novartis Ireland Limited
Tel: +353 1 260 12 55

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Novartis Farma S.p.A.
Tel: +39 02 96 54 1

Κύπρος
Novartis Pharma Services Inc.
Τηλ: +357 22 690 690

Latvija
Novartis Pharma Services Inc.
Tel: +371 67 887 070

Malta
Novartis Pharma Services Inc.
Tel: +356 2122 2872

Nederland
Novartis Pharma B.V.
Tel: +31 26 37 82 555

Norge
Novartis Norge AS
Tlf: +47 23 05 20 00

Österreich
Novartis Pharma GmbH
Tel: +43 1 86 6570

Polska
Novartis Poland Sp. z o.o.
Tel.: +48 22 375 4888

Portugal
Novartis Farma - Produtos Farmacêuticos, S.A.
Tel: +351 21 000 8600

România
Novartis Pharma Services Romania SRL
Tel: +40 21 31299 01

Slovenija
Novartis Pharma Services Inc.
Tel: +386 1 300 75 50

Slovenská republika
Novartis Slovakia s.r.o.
Tel: +421 2 5542 5439

Suomi/Finland
Novartis Finland Oy
Puh/Tel: +358 (0)10 6133 200

Sverige
Novartis Sverige AB
Tel: +46 8 732 32 00

United Kingdom
Novartis Pharmaceuticals UK Ltd.
Tel: +44 1276 698370

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